CICATRICIAL PEMPHIGOID

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A treatise submitted in partial requirement for
the degree of Master of Dental Surgery.

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1984.

CONTENTS

PREFACE

Lesions of the oral mucosa in general may be divided into two broad groups. In the first of these groups the lesions result from some local abnormality and there are no other systemic manifestations. In the second group, however, the oral lesion may simply represent a localized manifestation of some generalised disease process affecting the skin, other mucous membranes or apparently unrelated structures.

Although the oral mucous membrane is histologically similar to other lining mucosae it behaves in some respects as a modified form of skin and a considerable number of skin diseases show lesions in the mouth. The oral mucous membrane also bears considerable similarities, both histologically and immunologically, to the genital and ophthalmic mucosae. It is consequentially not uncommon for similar lesions to affect more than one of these structures.

The vesiculo-bullous disease, cicatricial pemphigoid, is one such condition in which lesions of a similar nature may affect both the skin and a variety of mucosal surfaces. Cicatricial pemphigoid is also a representative example from the growing list of diseases considered to be autoimmune in nature. It is therefore evident that anyone dealing with this condition must have a wide general knowledge of medical and surgical pathology extending well beyond the limits of the mouth itself.

This treatise presents a comprehensive review of the world literature to date concerning the condition cicatricial

pemphigoid. The chapters on diagnosis and treatment are, of necessity, dealt with in greater detail than the remainder of the treatise. However, the other chapters deal with related topics which assist in presenting a complete coverage of this condition.

Cicatricial pemphigoid has been defined as a disease process in its own right only since the early 1950's. The clinical presentation of this disease has been reported widely since then, but due to its autoimmune nature the cause and treatment of such a potentially damaging disease awaits absolute definition and will be the subject of much research in future years.

ACKNOWLEDGEMENTS

The author would like to express his gratitude to the following persons for their various contributions towards the production of this treatise.

Mrs. G.C. Mitchell

Associate Professor N.H. Smith - Department of Oral Medicine and Oral Surgery, Faculty of Dentistry, University of Sydney.

Dr. C. Lauer - Formerly, Department of Histopathology, Royal Prince Alfred Hospital, Sydney.

Mr. R. Johnson - Audio-Visual Department, Faculty of Dentistry, University of Sydney.

I TERMINOLOGY DEFINED

1. Cicatricial Pemphigoid
2. Vesicles and Bullae

I TERMINOLOGY DEFINED

1. Cicatricial Pemphigoid

The term "cicatricial pemphigoid" is used throughout, by the author, to describe the disease process under review in this treatise. The reason that this term is preferred is explained in the following discussion.

Prior to 1951 several terms were employed to describe the disease now known as cicatricial pemphigoid. These included chronic pemphigus, ocular pemphigus, pemphigus conjunctivae and benign mucous membrane pemphigus. The use of the word "pemphigus" is now quite unacceptable since the disease (cicatricial pemphigoid) does not represent a form of true pemphigus. Lever in 1951[115] and in his monograph in 1953,[116] on the basis of his histopathological studies, coined the term "pemphigoid", differentiating it from pemphigus, and described two variants: bullous pemphigoid and benign mucous membrane pemphigoid. It is the latter disease which corresponds to cicatricial pemphigoid.

The use of the word "benign" in Lever's terminology, in the light of our present understanding of the long term effects of the disease process, is perhaps not quite appropriate. Despite the fact that the prognosis in regard to life expectancy is good - in comparison to pemphigus vulgaris, and perhaps this is the distinction that Lever wished to make - the debilitating effects of the condition with respect to its chronicity and potential to cause scarring make it somewhat other than benign.

Oral and vaginal scarring are distressing; conjunctival scarring and corneal epithelialization leading to blindness are devastating. Despite the fact that not all cases lead to scar formation, the use of the qualifying term "cicatricial" rather than "benign" is in the author's view more appropriate if the full potential of the disease process is to be realized and understood.

It is the author's view also that the terms "mucosal" or "mucous membrane" need not be included. There are two forms of pemphigoid - the other being bullous pemphigoid. Bullous pemphigoid primarily affects the skin and only rarely the oral mucous membrane - the dermal lesions almost always appearing first. Ocular lesions have also never been reported. Apart from other distinguishing features, the lesions of bullous pemphigoid always heal without scarring. Thus if the two forms of pemphigoid are to be termed "bullous pemphigoid" and "cicatricial pemphigoid" and one refers to the latter then by exclusion one must be referring to that form of pemphigoid which classically always affects the mucous membranes (and occasionally the skin secondarily) and may lead to scarring of these surfaces, the terms "mucosal" or "mucous membrane" being redundant.

In more recent times several authors have described so-called variants of cicatricial pemphigoid and have coined terms to describe such variations.

In 1977 Forman and Nally[65] presented fourteen patients with recurrent blisters restricted entirely to the mouth. They coined the term "acquired oral non-dystrophic epidermolysis bullosa"

but considered it still to be a forme fruste of cicatricial pemphigoid.

Dahl[51] also described several cases of epidermolysis bullosa acquisita which he considered had features consistent with cicatricial pemphigoid and hence should be referred to as such.

Variations of cicatricial pemphigoid probably do occur. The author has observed personally several cases in which lesions are confined solely to the mouth (as reported by Forman and Nally). Currently and in the following review the term cicatricial pemphigoid is used to describe all cases diagnosed as such despite the severity or locality of the mucosal lesions.

2. Vesicles and Bullae

Vesicles and bullae are circumscribed collections of free fluid in the skin or mucous membranes.[217] In simple terms a bulla is simply a blister and there is no real difference between the meaning of this term and that of the term "vesicle".

However, "bulla" is usually used to describe larger blisters whereas "vesicle" is most commonly used to describe multiple-occurring small blisters. More specifically, in this review, lesions of less than one centimeter in diameter are considered vesicles, whilst those greater than one centimeter are considered bullae.

Vesicles and bullae may be intra-epithelial or sub-epithelial (vide infra), with their location being dependent upon the site

of cell damage involved in the developing process. Serum moves into the area of cell damage and forms the fluid collection seen clinically as either a vesicle or a bulla.

For some as yet unknown reason vesicles and bullae are unique to human beings and are not seen in any other mammals.[108]

II HISTORICAL REVIEW AND CLASSIFICATION

1. Historical Review

   (i) Early History

   (ii) The Renaissance of Medicine

   (iii) The Beginning of Modern Medicine

   (iv) Modern Medicine

2. Classification

II HISTORICAL REVIEW AND CLASSIFICATION

1. Historical Review

Despite the fact that a number of descriptions of cases of cicatricial pemphigoid have been recognized in the literature for many years, it has been only relatively recently that the disease was clearly defined.

It was not until 1951 that Lever,[115] on the basis of his histopathological studies, separated pemphigoid from pemphigus vulgaris. Prior to this time all such cases were thought of as being a variant of pemphigus, being variously reported under a number of titles such as ocular pemphigus, chronic pemphigus and pemphigus conjunctivae.[76]

The following brief historical review traces the evolution of thought encompassed in the works of the more important personalities responsible for our present understanding of the clinical and pathological processes of cicatricial pemphigoid.

(i) Early History

The initial occasion the word pemphigus was recorded was by Hippocrates (460-370 B.C.) in 400 B.C.[56,118] He enumerated several different types of fevers and used the term to describe one such fever as pemphigoid fever (pemphigoides pyretoi), which was described as terrible in its appearance.[116] This term signified something related to the original connotation of the word "pemphix", which was air, breath or puff. Hippocrates

believed that the lesions he described on the skin were produced by air breathed up through the skin causing blister formation.

Lever[116,118] has, through careful examination of the reports of Hippocrates, concluded that the pemphigoid fever he refers to does not in fact correspond to the modern day understanding of true pemphigus, and that as a disease it was therefore unknown to him.

Galin[56] in 200 A.D. spoke also of the fevers of pemphigoides: "by expansion of the heat generates pustules in the mouth". Again Lever[116,118] believes that this description is not that of true pemphigus.

The medieval writers adhered closely to the writings of the great Greek and Roman physicians and rarely added clinical observations of their own. No description of a disease resembling pemphigus was found by Lever in the medieval European literature.[118]

(ii) The Renaissance of Medicine (Sixteenth to early Eighteenth Century)

The uncritical style of copying the Greek and Roman medical writers was continued well into the Renaissance.[118] It is readily understandable that the confusion in most of the early literature was almost certainly caused by men reporting cases or reviewing the work of another person who had written years before. The identical terminology was used despite the lack of correspondence to signs and symptoms, and hence errors in diagnosis were perpetuated.

In Lever's opinion[116,118] Sigismond Koenig, of Berne, Switzerland, in 1681 described the first unquestioned case of

pemphigus. No name was given by Koenig to the disease. However, three episodes of a generalized bullous eruption over a period of eight months for the first attack with new bullae appearing continuously is highly suggestive of a diagnosis of pemphigus vulgaris. The patient described by Koenig, probably the first one with pemphigus to be recorded in medical history, survived.

In 1730 De Sauvages[56] wrote a classification of diseases which included pemphigus by name. Despite the fact that the disease he attributed as being pemphigus was almost certainly a viral illness, he was the first writer to classify bullous disease and employ the name of pemphigus. Consequently the definition given by De Sauvages was generally accepted and hence most diseases described as pemphigus in the following years were bullous eruptions of short duration.[118]

(iii) The Beginning of Modern Medicine (late Eighteenth and Nineteenth Centuries)

The next author after Koenig to report a true case of pemphigus is believed by Lever[116,118] to be David Macbride (1726-1778). In the second edition of his book, published in 1777, he discussed four cases of pemphigus. It is evident that the cases described by Macbride were instances of pemphigus vulgaris as the type of lesions, their duration, severity and the description of the disease as "most tedious and distressing" suggest this diagnosis.[56,116,118]

It is noteworthy that previous to 1789 none of the eruptions described as pemphigus corresponded with the modern conception of the disease, since all were benign bullous eruptions of short duration. On the other hand, the two writers Koenig and Macbride who had reported true cases of pemphigus had not used this term in their diagnosis.

An important progressive step was made by Wichmann(1740-1802) who, in a lecture delivered on February 3rd, 1791 before the Akademie Nűtzlicher Wissenschaften in Erfurt, Germany, stated that true pemphigus was always a chronic disease and not always febrile, as almost all previous writers had assumed.(118) The evidence for this conclusion was based on the observation of a case which he described in remarkable detail. The condition was pemphigus vulgaris, its characteristic features being: flaccid bullae in most instances, occasionally no bullae at all but merely detachment of the epithelium from the corium leading to the development of large denuded areas, severe involvement of the oral mucosa with extension onto the lips and a fatal outcome.

It is to Wichmann that we also attribute the first description of a case of cicatricial pemphigoid in 1794.(76,116,125,186,187) He described the case as follows:(116)

"For three years an unfortunate female patient has been suffering from this malady so that from time to time blisters appear, mainly on chin and chest. The unconquerable poison has destroyed both eyes, and although in the last year the blisters have become always rarer and smaller, the whole oral cavity and especially the lips are completely denuded of epidermis".

The chronic and benign course, the destruction of both eyes, the extent of the oral lesions and the minimal cutaneous involvement all point in Lever's[116] mind to a diagnosis of cicatricial pemphigoid. Despite this description, Wichmann did not give the condition a name.

During the first three decades of the nineteenth century the name pemphigus was used to designate a variety of bullous eruptions as well as the specific disease entity. The opinion was frequently expressed that where there are bullae there is pemphigus.[118] At this time the Parisian school was the outstanding school of dermatology in Europe. Despite the fact that the English did not necessarily share the catholic view of pemphigus that the French had, their school retained uncontested leadership until well into the middle of the nineteenth century. It is perhaps for this reason that many years passed between Wichmann's description and the next recorded cases of cicatricial pemphigoid.

(iv) Modern Medicine (late Nineteenth Century up to the present)

The second case of cicatricial pemphigoid was recorded by Cooper in 1858.[116,118,205] In fact he is attributed as being the first to describe the ocular manifestations of the disease. Cooper's patient had blisters on the skin as well as on the conjunctivae. While the cutaneous lesions healed after a few months without scarring, the conjunctivae remained inflamed and subsequently scarred badly.

Subsequent writers hesitated to label as pemphigus those eruptions which included only ocular lesions. So it was that von Kries in 1878[116,118,205] proposed the name "essential shrinkage of the conjunctiva".

In the years immediately following, the majority of observers were in favour of regarding essential shrinkage of the conjunctiva as a manifestation of pemphigus and employed such names as "ocular pemphigus" or "pemphigus conjunctivae".

Combinations of oral and conjunctival lesions were also reported by Morris and Roberts,[141] Fox[68] and Nettleship.[144] In all these patients, however, with lesions on mucous membranes or even cutaneous lesions in addition to ocular lesions, the diagnosis of pemphigus was rarely, if ever, contested.

It is to Thost that we owe the first detailed description of cicatricial pemphigoid as well as the original nomenclature. In 1896 and in subsequent papers, he wished to distinguish between an "acute pemphigus of mucous membranes" usually seen in pemphigus vulgaris, foliaceus and vegetans and a "chronic pemphigus of the mucous membrane" which leads to scars in the course of years.[118] He noted that with the chronic form of pemphigus of the mucous membranes there were always conjunctival scars and in most cases cicatrices in the mucous lining of the nose, mouth, larynx and oesophagus. He also emphasized the benignness of the condition, which had never been fatal in his experience.

In 1911 Thost first used the term "benign mucous membrane pemphigus" and listed its salient features as follows:[186,187]

" i) Exclusive participation of the mucous membrane and total freedom on the part of the skin surface, with only very exceptional extension of the mucous membrane to directly adjacent skin areas.

" ii) Very regular participation of the connective tissue of the eye which leads to essential shrinking thereof and later to phthisis bulbi.

" iii) There is always a tendency for the growing together of adjacent parts of the mucous membranes and for shrinkage of deeper structures of the mucous membranes.

" iv) A chronic feverless course.

" v) Concurrent general cachexia and poor nutrition of the skin and poor development of the muscles.

" vi) Completely unaffected by medication, especially iodine and mercury. Wassermann negative."

In summary, Thost indicated: "There are, in short completely different diseases of the skin and mucous membrane which have in common the symptom of blister formation of the upper strata. The cases of chronic mucous membrane pemphigus are distinguished from the many forms of pemphigus by a very particular course. They

represent in all cases a very definite and in all cases an identical disease pattern which is sharply characterized by its course and localization."

In spite of Thost's many publications the disease continued to be known as ocular pemphigus, chronic pemphigus, or pemphigus conjunctivae.[76] That the disease Thost had described was in fact a different condition from pemphigus was definitively established by Lever in 1951.[115] On the basis of his histopathological studies, cicatricial pemphigoid (or benign mucous membrane pemphigoid as he termed it) was separated from pemphigus vulgaris. He clearly demonstrated that the bullae of benign mucous membrane pemphigoid were sub-epithelial whereas those of true pemphigus were intra-epithelial and characterized by acantholysis. In addition he emphasised that the prognosis for life was vastly different in the two conditions.

It was in fact Lever who reported the first large series of cases of cicatricial pemphigoid - thirty cases in his 1953 monograph.[116] In this he clearly described the clinical and histological pictures of cicatricial pemphigoid.

In the thirty years since Lever's work[116] great progress has been made in the understanding and in the treatment of cicatricial pemphigoid.

In the late 1950's came the introduction of the corticosteroids into the treatment of cicatricial pemphigoid.[117] This great milestone has vastly improved the prognosis of the disease and has also lead to a better quality of life for the patients so afflicted.

The use of corticosteroids also opened the way for the introduction, in more recent years, of the cytotoxic drugs such as azathioprine in the treatment of cicatricial pemphigoid. As is discussed in a later section this drug has greatly improved the prognosis of the disease as far as arresting the disastrous effects of the ocular lesions of cicatricial pemphigoid is concerned.

The original and subsequent immunofluorescent studies of mucosa and sera from persons with cicatricial pemphigoid failed to reveal basement-membrane zone antibodies which are present in almost all cases of bullous pemphigoid.[28] However, in 1972, Bean et al[17] presented the initial evidence for the cause of cicatricial pemphigoid. By studying specimens of skin, conjunctiva, and oral mucosa from active cases of cicatricial pemphigoid they were able to demonstrate the existence at the basement-membrane zone of in-vivo-fixed immunoglobulins morphologically identical to those found in bullous pemphigoid. However, they were unable to find circulating antibodies to the basement-membrane zone. It was Dantzig[54] in 1973 who first demonstrated the presence of circulating antibodies directed against the basement-membrane zone in a patient with cicatricial pemphigoid.

The use of immunofluorescence in cases of cicatricial pemphigoid has added another diagnostic tool which further corroborates the histopathology as a means of verifying the diagnoses. It has also advanced the autoimmune cause of the disease and has supplied evidence towards rational therapy.

In 1971 Susi and Shklar[203] detailed the initial report on the ultrastructure of the lesions of cicatricial pemphigoid. This and subsequent publications have contributed greatly to the understanding of the mechanism of bulla formation in cicatricial pemphigoid.

Finally, several lines of investigation that might lead to a more complete understanding of cicatricial pemphigoid may be outlined at this point. Firstly, immunoelectronmicroscopic studies would help localize more precisely the tissue-fixed immunoglobulins and complement in cicatricial pemphigoid. Secondly, screening sera from patients with cicatricial pemphigoid against various substrates with particular emphasis on human mucous membrane would be desirable. These studies would assist in determining whether the incidence of circulating antibasement-membrane zone antibodies can be demonstrated and would provide more information about the organ and species specificities of these antibodies. Finally, elution studies in which basement-membrane zone immunoglobulins from lesions of cicatricial pemphigoid could be extracted and reacted with mucous membrane from the same patient. This would establish whether the tissue-fixed immunoglobulins are indeed autoantibodies.

2. Classification of Bullous Diseases

As the bullae of many of the blistering diseases may be indistinguishable clinically, the most useful classification is based upon the location of the bullous cavity within the epithelium.

Bullae, on these grounds, may therefore either be intra-epithelial or sub-epithelial. Occasionally a mixed type may occur.

The intra-epithelial bulla forms entirely within the epithelium which therefore forms its roof, floor and sides. This type of bulla most commonly results from degenerative changes in the spinous cell layer of the epithelium. It is important to note that in this type of lesion diagnostic epithelial smears may be obtained.

The sub-epithelial bulla results from a separation of the basal layer of the epithelium from the underlying connective tissue. In these instances the roof and sides of the bulla are formed by epithelium whereas the floor consists of connective tissue. Epithelial smears from these bullae usually show a few normal epithelial cells and many inflammatory cells from the connective tissue, and hence are virtually non-diagnostic.

The mixed type is not a primary form of bulla but may arise from either the intra-epithelial or sub-epithelial types by means of degeneration or repair.

On the basis of the above discussion several of the well known vesiculo-bullous eruptions may be classified as either being intra-epithelial or sub-epithelial.

<u>Intra-epithelial bullae</u>

Herpes simplex

Herpes zoster

Pemphigus vulgaris

<u>Sub-epithelial bullae</u>

Erythema multiforme

Cicatricial pemphigoid

Bullous pemphigoid

Bullous lichen planus

III DIFFERENTIAL DIAGNOSIS

1. Pemphigus Vulgaris

2. Bullous Pemphigoid

3. Bullous Lichen Planus

4. Erythema Multiforme

5. Muco-ocular Ulceration

   (i) Behçet's Syndrome

   (ii) Reiter's Syndrome

6. Viral Diseases

   (i) Herpes Simplex

   (ii) Herpes Zoster

   (iii) Herpangina

III DIFFERENTIAL DIAGNOSIS

Introduction

Significant advances have been achieved in recent years in the understanding of the nature of many of the common mucous membrane diseases.(184) Whilst the exact aetiology of many of these conditions remains still to be adequately clarified, there has been considerable progress in our knowledge of the characteristic tissue changes of a variety of oral mucosal lesions.

Vesiculobullous lesions of the mucous membranes do not infrequently present the clinician with a difficult and often bewildering challenge in diagnosis. Perhaps this is partly so because bullae by themselves have no macroscopical structural features of diagnostic value.(44) The character of most primary lesions and bullae in particular is never so distinct on the mucous membranes as on the skin because of the modifying influence of heat, trauma, moisture and secondary infection, and the absence of a keratin layer. In fact bullae are only occasionally observed on the mucous membranes - another factor making their differential diagnosis quite difficult. The transient nature of these lesions results in early rupture and alteration of the clinical appearance to that of a non-specific ulcer.

A careful history and thorough physical examination are especially important in selecting the appropriate pathological entity from a number of conditions that may produce similar mucosal ulceration. The final diagnosis may also require

confirmation by histopathological examination and immuno-fluorescent antibody studies.(131)

If and when an intact bulla is observed, a careful clinical examination will assist greatly in its differential diagnosis. By observing the following lesional characteristics a diagnosis may be more easily made.(140)

* The location of the lesions
* The type of bullae
* The rapidity with which the bullae burst
* Pressure with the finger on the roof of the bullae
* The appearance of the bullae and the type of demarcation surrounding the lesions
* Scar formation
* Race of the patient
* Nikolsky sign
* Age of the patient

The oral lesions of cicatricial pemphigoid will be discussed under these headings in a later section.

In considering the differential diagnosis of cicatricial pemphigoid, every chronic vesiculobullous disorder of the mucous membranes must be included.(11) However, there are in general only a small number of conditions that may be confused more commonly with cicatricial pemphigoid, especially during the early phases of the disease. The conditions are:

* Pemphigus vulgaris
* Bullous pemphigoid
* Bullous lichen planus
* Erythema multiforme
* Muco-ocular ulceration (Behçet's Syndrome, Reiter's disease)
* Viral diseases (Herpes simplex, Herpes zoster, and Herpangina)

1. Pemphigus Vulgaris

Pemphigus vulgaris is a serious, often fatal, vesiculo-bullous disease, of autoimmune aetiology which affects the skin and mucous membranes.(5,18,162)

Pemphigus vulgaris tends to be a disease of middle age.(71,162) It seldom appears before the age of thirty years and reportedly has its highest incidence in the forty to sixty age group.(5,37,71,133,179,214,217,225) Either sex may be affected equally.(5,162,179,183,225) It has been suggested that pemphigus vulgaris is a "Jewish disease" being also significantly higher in the Ashkenazian group of this race.(71,162,214) Apart from this high incidence amongst Jewish people, Mediterranean races also show a predisposition to the disease.(5,179,225) Despite these findings, all ethnic groups show a susceptibility.(179)

When cicatricial pemphigoid commences with oral vesicles and erosions, a diagnosis of pemphigus vulgaris should be considered.(14) Approximately 50 percent of patients with

pemphigus vulgaris will develop their initial lesions in the mouth.[71, 179,225] The lesions, unlike those of cicatricial pemphigoid, do not remain localized and the entire oral mucosa rapidly becomes involved.[186] In fact virtually all pemphigus patients have oral lesions at some time during the course of their disease.[14,127,185] The skin soon becomes involved with lesions being usually quite extensive. Desquamative gingivitis and conjunctival involvement are often common features of the disease.[14,125,186]

The bullae of pemphigus are characteristic and have a number of features which distinguish them from those of cicatricial pemphigoid. They tend to be more superficial and widespread.[124] The bullae are also thin-walled, flaccid, and spreading, rupturing easily to leave large eroded and denuded surfaces.[44,125,133,217] These large areas of denudation are surrounded by a whitish collar of advancing detachment of the epithelial layer.[179] The dermal lesions may occur anywhere on the body but have a predilection for areas of pressure.[217]

The histological appearance of a lesion of pemphigus characteristically shows supra-basal vesiculation, with the basal cell layer remaining intact and attached to the underlying connective tissue. The characteristic finding of acantholysis is diagnostic for pemphigus.[133,185] The appearance of Tzank cells in the contents of a fresh bulla is also pathognomonic of the condition.[5,71,217]

The extension of a blister by slight pressure or the formation of a new blister by firm tangential pressure of a finger on the

intact epidermis (or epithelium) of a patient with pemphigus vulgaris is a valuable diagnostic aid (Nikolsky's sign). The explanation for this phenomenon is found in the acantholytic process.[5,179,217] Because of the superficial location of the lesion, scar formation is not a feature of the healing process and is a useful diagnostic feature.[179]

The presence of intercellular antibody on stratified squamous epithelium is readily demonstrated in almost 100 percent of patients, by both direct and indirect immunofluorescent methods,[19,71,225] the titre of antibody usually being proportional to the severity of the disease.[71,185]

Before the advent of cortisone the disease was invariably fatal within one year of the onset of symptoms.[5,44] Even with the administration of corticosteroids and occasionally cytotoxic agents, the disease may still prove fatal in a small percentage of severe fulminating cases.[133,217]

2. Bullous Pemphigoid

Bullous pemphigoid is a chronic, relatively benign, and often self-limiting condition of autoimmune aetiology.[133] The differential diagnosis from cicatricial pemphigoid may be difficult at times because of many similar features. For this reason Shklar and his co-workers[189] have suggested that bullous pemphigoid and cicatricial pemphigoid are indeed variants of a single entity, being at opposite poles of a disease spectrum.

Bullous pemphigoid has many features in common with cicatricial pemphigoid. Bullous pemphigoid is primarily a disease of the elderly, with the majority of patients in the 60-70 age group.[16,29.173,179,183,196] Despite this the disease may also occur in children.[16,29,183,190] Like cicatricial pemphigoid, the bullae of bullous pemphigoid are sub-epithelial and are microscopically indistinguishable from the former disease. Consequently the bullae of the two disease have the same clinical characteristics, being tense, thick-roofed and surrounded by an erythematous halo.

Despite these similarities there are some features of bullous pemphigoid of distinction. There appears to be no sex predilection - males and females being equally affected.[173,179,183] The characteristically distinctive feature of bullous pemphigoid is that oral lesions occur only rarely, and if they do, then they occur late in the progress of the disease and are transitory in nature.[173,189,196] Oral lesions occur in between 20 and 30 percent of cases and are a presenting feature in less than 10 percent of patients.[29,133,179,188,217] If oral lesions do occur they are small, rupturing and healing readily without scar formation.[29,179] Conjunctival involvement is not a feature of the disease.

The lesions of bullous pemphigoid always and most often primarily occur on the skin and are large, tense and have an irregular outline. They predominantly affect the lower abdomen, groin, axillae and flexor surfaces of the arms and legs. [16,133,173,179,217] The lesions, when they rupture, show

a tendency to heal rapidly without scarring which is in contrast to the dermal lesions of cicatricial pemphigoid.[29,133,196]

Since the light microscopic appearances of bullous pemphigoid are indistinguishable from those of cicatricial pemphigoid, immunofluorescent studies have served to differentiate the two conditions.[217] Using the direct immunofluorescent technique, Jordon and his associates[100] demonstrated antibodies directed toward the basement membrane area. Using the direct technique it is expected that almost 100 percent of patients with bullous pemphigoid will show a positive result. Antibodies directed towards the basement area in the serum of patients with bullous pemphigoid can be found in approximately 60 percent of patients.[16,29,188,217]

Bullous pemphigoid would appear to respond more readily to corticosteroids and cytotoxic agents with oral lesions (if present) being somewhat resistant to such therapy.[29,179,189,217]

In view of similar light microscopic appearances, combined with immunofluorescent findings of a similar yet statistically divergent nature it appears probable that bullous pemphigoid and cicatricial pemphigoid are variants of a similar disease process.

3. Bullous Lichen Planus

This is a rare form of lichen planus which, in some cases, is extremely difficult to differentiate from cicatricial pemphigoid. Cooke[44] has classified it as a sub-epithelial vesiculobullous disease. The so-called erosive form of lichen planus may begin as this type of bullous eruption and not as a progressive process from

non-erosive lichen planus.[183] Nevertheless the bullous form of the disease may resemble erosive lichen planus when the bullae rupture due to their delicate transitory nature. Estimates of the incidence of bullous oral lichen planus lesions range from 2 percent to over 50 percent of cases of oral lichen planus.[72]

Clinically the gingivae may present a diffuse desquamating inflammatory condition similar in appearance to the desquamative gingivitis commonly observed in cicatricial pemphigoid.[187] Following rupture of the mucosal vesicles the eroded or frankly ulcerated lesions are irregular in size and shape and appear as raw and painful areas in the same general sites involved by the simple form of the disease.[183] Despite the erosions of the mucous membrane, if the oral lesions are observed closely, the characteristic radiating striae may usually be noted at the periphery of the individual lesions. The presence of characteristic violaceous skin lesions will also serve to aid in a confirmatory diagnosis.

In comparison to cicatricial pemphigoid the lesions of bullous lichen planus develop slowly, their course being prolonged, and with the patient usually demonstrating an absence of any constitutional symptoms.[125,186] Lichen planus, however, does not cause any ocular symptoms.[125,186]

Biopsy studies would appear to be most helpful in differentiating bullous lichen planus from cicatricial pemphigoid. In lichen planus the two pathognomonic histological features are a liquefaction degeneration of the basal cell layer and a band-like infiltrate of lymphocytes into the papillary level of the connective

tissue. The basal cell layer is intact in cicatricial pemphigoid.

On the occasions when severe and extensive oral ulceration or desquamative gingivitis lack the characteristic clinical and histopathological features of lichen planus, immunofluorescent studies of the lesions may reveal characteristic findings which may contribute to a definitive diagnosis. Direct immonufluorescent examination exhibits linear fibrin as well as immunoglobulin deposits at the epithelial-connective tissue junction.[72] In addition, cytoid bodies are seen in the form of ovoid or globular fluorescent immunoglobulin deposits located in the papillary corium adjacent to the epithelial-connective tissue junction. Although this pattern of immunofluorescence is not specific for lichen planus it is significantly different from that of cicatricial pemphigoid.

The use of topically applied corticosteroids usually affords symptomatic improvement, often causing the oral lesions to diminish and sometimes to clear up rapidly and completely.[37]

4. Erythema Multiforme

Erythema multiforme is a recurrent, vesicular, chronic mucocutaneous inflammatory disease.[121] Clinically the condition may show extremely variable features which can mimic other diseases. Nevertheless, from the natural history, the clinical findings, and the histological picture, it is usually possible to rule out other conditions and therefore arrive at a definitive diagnosis.

Several authors have attempted to classify erythema multiforme into certain distinctive clinical patterns depending upon the clinical manifestations. Cohen and Randell[43] classify the disease as "minor" or "major" (Stevens-Johnson Syndrome), whereas Al-Ubaidy and Nally[4] describe three different patterns: a papular or complex form (skin only); a vesiculobullous form (skin and mouth); and a severe bullous form, each representing a progressively more severe variant of the one disease process.

The disease usually affects young adults,[5,43,133,183] with males being afflicted more often than females.[11,37,183] The precise aetiology of the condition is unknown although it is thought to be of autoimmune origin.[43,133,214] Approximately 50 percent of cases are known to be precipitated by a variety of agents: herpes simplex infection, systemic diseases, drugs, bacterial infections, radiation therapy and malignancy.[4,11,43,121,183]

The disease may affect the mucous membrane and the skin independently or simultaneously.[121] Intraorally the labial mucosa is usually extensively involved as well as the tongue, palate and buccal mucosa. The gingiva is infrequently involved. Oral bullae are found only rarely as they rapidly become macerated and thus appear as ulcerated areas. The mouth and lips become characteristically swollen and show haemorrhagic crusting.[5] The pharynx, trachea and bronchi may be similarly affected.[11] The lesions heal in a few days or weeks without scarring despite their recurrent nature.[4,5,11,44]

In its severe form, erythema multiforme may affect the eyes, the most common changes being a catarrhal or purulent conjunctivitis.[4] However, these lesions may range from a mild conjunctivitis, terminating without sequelae, to severe conjunctival blistering, pseudo-membrane formation affecting portions of the bulbar and palpebral conjunctiva, and lid oedema. Secondary infection producing purulent conjunctivitis may ensue. Symblepharon and even ankyloblepharon may develop and produce corneal dessication as in cicatricial pemphigoid.[11,207] Unlike the oral lesions of erythema multiforme, the ocular lesions heal with scar formation.[11]

The presence of skin lesions will undoubtedly provide a confirmatory diagnosis of the oral mucosal lesions. The typical dermal lesions are seen most frequently as being symmetrically distributed on the extremities - the back of the hands, palms, wrists, forearms, feet, elbows, and knees - and less often on the face, neck and trunk. The lesions appear as dull red papules which gradually enlarge to attain a red periphery and cyanotic centre. These are the characteristic "target lesions".[4,11,43,183] New lesions develop in crops, each disappearing in several weeks without scarring.[5]

Several other features also serve to help differentiate this condition from cicatricial pemphigoid. Erythema multiforme tends to have an explosive onset but is also a recurrent self-limiting process. Prodromal symptoms such as fever, malaise, headache and transient joint pain may occur in the more severe forms.[11] During the first few days of each attack the patient is usually

febrile and in great discomfort from oral lesions, so much so that speaking and eating are very difficult.[44,121] Regional cervical lymphadenitis may also commonly occur.[4,44,183,214]

There are no characteristic histological features diagnostic for erythema multiforme.[4] Diagnosis on histological grounds is usually made by exclusion of other diseases.[44] Various features such as eosinophilic degeneration of the spinous cell layer[44] (causing intra-epithelial vesiculation), sub-epithelial bulla formation,[43] oedema of the superficial connective tissue,[183] dilatation of superficial capillaries and lymphatics, and perivascular lymphocytic infiltration in the deeper layers of the connective tissue[31] have been reported.

It appears that although the condition is self-limiting, corticosteroids used for short periods may have a profound effect[4] on the lesions themselves without altering the predilection for the disease to recur.[121]

5. Muco-ocular Ulceration

(i) Behçet's Syndrome

Behçet[164] reported the triad of recurrent oral and oculogenital ulceration which now bears his name. The syndrome comprises single or multiple, long lasting, painful aphthous lesions of the oral mucosa or sharply circumscribed, ulcerated aphthae of the genitals and inflammatory changes of the eyes. Other commonly associated symptoms include skin lesions, arthritis, gastrointestinal problems, neurological lesions, and lesions of

the blood vessels.[37,164,183]

The diagnosis of the condition is usually established in the early years of adolescent life as the disease is primarily one of young persons.[181] The syndrome usually begins between 10 and 30 years of age.[164,183] Males are much more frequently affected than females[164,183] and the incidence is reportedly higher in certain geographic areas and in certain races, mainly originating from the Eastern Mediterranean countries and Japan although the significance of this factor is probably minor.[142]

The oral lesions which are usually the first manifestation bear striking similarities to the mild and severe forms of recurrent aphthous ulceration.[37,164,183] They may occur at any site but primarily on the lips, tongue, buccal mucosa, soft and hard palates, tonsilar region, pharynx and nasal cavity. The ulcers may be single or multiple, usually up to one centimeter in diameter, and are well differentiated from the surrounding mucosa by a peripheral erythematous halo. The lesions also have a covering of a yellow or greyish exudate on their base. The ulcers are extremely painful and will almost certainly make eating difficult. They are recurrent in character and often heal with scar formation.[181,207]

The disease affects the genital region in the form of multiple, recurring herpetiform or aphthous-like ulcers (generally smaller than the oral lesions).[164,181,183,207] In the male the scrotum, root of the penis or urethra may be affected. In the female the sites involved are the vulva, vagina and cervix. The lesions may

also be found in both sexes on the genitocrural fold, the anus, and the perineum, or in the rectum.[164] Unfortunately, the lesions may result in necrosis which can lead to severe scarring on healing.[207]

Except for the ocular changes that may occur, Behçet's Syndrome is essentially benign. The ocular involvement occurs mostly after the oral and genital lesions have arisen.[207] Both eyes are eventually involved and the presenting symptoms are those of intense peri-orbital pain and photophobia.[164,183] The manifestations of the disease include corneal ulceration, vascular changes, paresis of the ocular muscles and bleeding into the vitreous. They may range from a simple conjunctivitis (early) to uveitis and finally hypopyon (late).[183] Iridocyclitis is also frequently seen.[37,164] The important changes occur in the uveal tract, that is the iris, the ciliary body and the choroid.[207] Here early inflammatory signs - relapsing iridocyclitis and anterior uveitis - often apparently of little significance, progress inexorably over a period of years and may lead to blindness (usually from optic atrophy and secondary glaucoma).[164,181]

Several theories have been proposed for the aetiology of Behçet's Syndrome. Viral,[142,164,183] hormonal,[37,183] and psychogenic[207] factors have been suggested. However, a number of findings would suggest that the disorder may have an auto-immune basis.[87,142] Lehner[109] has shown that the oral epithelium or a cross-reacting microbial antigen can stimulate humoral and cell-mediated responses which include epithelial

destruction. The antigenic component of oral squamous epithelium would appear to be the cytoplasm of the prickle cells.[142]

The histological appearances of oral ulcers, although non-specific, may be indispensable as far as excluding other diagnoses. In the first few hours a heavy infiltration of lymphocytes is observed but after 18 hours neutrophils tend to predominate and with mononuclear cells give a picture of non-specific chronic inflammation. Vasculitis in the form of perivascular infiltration with an endovasculitis type of endothelial proliferation that obliterates the lumen is also a common finding.[164,183]

The dramatic response of the majority of cases to corticosteroids and the beneficial results of other immunosuppressive agents also support the theory that Behcet's Syndrome is of autoimmune origin.[109,164,181]

Two important points should be considered when clinically differentiating cicatricial pemphigoid from Behcet's Syndrome. The lesions of Behcet's Syndrome are ulcerative and erosive rather than bullous, and also desquamative gingivitis is not a feature of Behcet's Syndrome.

(ii) Reiter's Syndrome

Reiter's Syndrome, in this discussion of the differential diagnosis of cicatricial pemphigoid, is briefly described only for completeness.

Classically the disease consists of a tetrad of manifestations: nongonococcal urethritis, conjunctivitis, subacute or chronic polyarthritis and mucocutaneous lesions.[183] In any given case

the full tetrad is often not present.

Reiter's Syndrome is almost totally confined to males, usually between 20 and 30 years of age.

The urethritis clinically mimics gonorrhea and the discharge is usually associated with an itching, burning sensation. The polyarthritis is often bilaterally symmetrical. The conjunctivitis is very mild and may be easily overlooked. Cutaneous lesions consist of red or yellow keratotic macules or papules which eventually desquamate, somewhat similarly to those of psoriasis.

The oral lesions may be present in up to 50 percent of patients, Shafer and his associates[183] describing them as painless, red, slightly elevated areas sometimes granular or even vesicular, with a white circinate border. They occur most commonly on the buccal mucosa, gingiva and lips. Lesions which occur on the tongue resemble those of erythema migrans whilst those on the palate appear as bright red purpuric spots.

Histologically the lesions show parakeratosis, acanthosis and polymorphonuclear leukocyte infiltration of the epithelium.[183] Microabscess formation (similar to that of psoriasis) is also occasionally seen in the epithelium.

Pleuropneumonia - like organisms and also a Bedsonia group virus have been implicated as possible aetiological agents.

Treatment consists of antibiotic and corticosteroid administration. As with Behçet's Syndrome, if oral lesions alone are present, Reiter's Syndrome may be difficult to differentiate from cicatricial pemphigoid but with the development of the other classical clinical manifestations the diagnosis is made easily.

6. Viral Diseases

(i) Herpes Simplex

Herpes simplex, an acute infectious disease, is probably the most common viral illness affecting man, with the exception of the viral respiratory infections.[183]

The causative agent, the herpes simplex virus (Type I) is referred to as being dermatropic because of the necessity for it to reside within cells of ectodermal origin (skin, mucous membranes, eyes, central nervous system).[183] The herpetovirion is an icosahedral DNA virus which multiplies in the nuclei of infected cells.[5]

The first encounter with the virus in a non-immune subject is known as the primary infection. This produces an immune response, both humoral and cellular, which usually protects the individual against reinfection with the same virus. However, the herpes virus has the property of remaining quiescent in the host for many years but reactivation of the latent virus (by various stimuli) may occur, producing a recurrent illness.

The history of a primary infection is characteristic. The primary illness may occur in either sex, at any age,[133] although most cases occur in early life - between the ages of one and six years.[214] If adulthood has been reached without herpetic infection the primary lesion may present at any time, although predominantly in young adults.[183,214] Cawson[37] believes that it is being seen increasingly often in adolescence and adults and less often in children.

Typically there is a 2 to 3 day prodromal period during which fever (temperatures between 38°C and 39°C) and malaise together with submandibular lymphadenitis occur.[5,44,214] This early involvement of lymph glands which are enlarged and painful is an important diagnostic feature.[214] Within a few days the mouth becomes painful and the gingiva intensely inflamed (this feature being less marked in adults).[183] The development of vesicles anywhere in the mouth rapidly follows. Local erythema and oedema, accompanied by itching and burning sensations precede the appearance of these small, uniform, tightly clustered vesicles.[133] The vesicles contain a clear fluid which turns cloudy after a few days. In a short time the vesicles burst and form shallow, ragged, extremely painful ulcers covered by a grey pseudomembrane and surrounded by an erythematous halo. Apart from the rest of the oral cavity, the lips are usually affected by these lesions and on the vermillion borders the crusts covering the erosions become blood-stained and, as they dry, become stuck to the opposing lip.[44] The mouth is extremely sore and stagnation may occur with a non-specific halitosis. The disease is self-limiting and runs a 7 to 10 day course of pain and discomfort with gradual subsidence of some 3 to 4 days. The oral lesions heal completely without scarring.[5,44,133]

Although a herpetic conjunctivitis may occur, the cornea is the main site of herpetic infection.[207] There are two types of herpetic keratitis. The most common is dendritic keratitis, a very acute and painful condition. The other type is disciform keratitis which results in a round disc-shaped opacity in the

deeper layer of the cornea. Whilst the former type heals with no visual impairment, the disciform type, which is much less acute, often leaves large deforming opacities.

On histological examination, the basic injury is to the parabasal and intermediate epithelial cells.[133] The vesicle itself is intraepithelial,[44,183] as a result of acantholysis. Within the vesicle there are many cells showing ballooning degeneration of the nuclei, and many multinucleated epithelial cells representing fusion of adjacent infected cells. Occasionally intranuclear inclusion bodies are seen.[5,183,214] The virus may also be cultured from vesicle fluid.[166] Serum viral antibody titres may also be shown to rise to a peak over a period of about 10 days. Exfoliative cytology is perhaps the most useful and rapid diagnostic test.[5,214] Changes seen in the oral mucous membrane cells are ballooning degeneration of the nucleus, multinucleation of cells and early margination of the chromatin.

It is estimated that 30 to 50 percent of patients will suffer from recurrent lesions.[5,37,183,214] These recurrences rarely occur in the mouth but affect the skin around the mouth. The condition is familiarly known as cold sores. These lesions develop and heal similarly to those of the primary illness, with symptoms, however, being much less severe, and restricted.

Treatment, because the condition is self-limiting, consists of reassurance, use of analgesics, dietary advice, and the use of chemotherapeutic agents which act on the virus within the cell nucleus.

(ii) Herpes Zoster

This is a viral infection characterized by severe pain, a vesicular rash and stomatitis in the area of distribution of a sensory nerve.(37) The trigeminal nerve may therefore be involved. In a well developed case there can perhaps be no easier diagnosis, for the unilateral distribution of the vesicles on the skin and mucosa is unique.(44)

Herpes zoster usually affects adults, often of middle age or over.(37,183,214) The first sign is severe pain and irritation in the skin area corresponding to the nerve affected. Malaise and fever also develop. Vesicles soon develop on the face and in the mouth up to the mid-line. When the ophthalmic division of the trigeminal nerve is involved the eye may be severely affected.(214) A severe iridocyclitis and secondary glaucoma may occur.(207)

Within the oral cavity the lesions appear much as those of herpes simplex but are restricted to a particular nerve distribution.

The lesions of herpes zoster fade over a relatively long period and there is often considerable systemic upset. A most important eventual complication is post-herpetic neuralgia occurring in the area of the rash.(214) It is also apparent that when the second and third divisions of the trigeminal nerve are affected there is a great liability for the geniculate ganglion to be affected as well, with a resulting lower neurone paralysis.(44)

Histological and cytological examination of the lesions of herpes zoster are indistinguishable from those of herpes simplex.[37,44] Treatment of the disease is also essentially the same as for herpes simplex. Recurrences do not occur.[207,214]

(iii)Herpangina

Herpangina is a relatively mild viral infection caused by the Coxsackie A4 type virus. It most frequently affects children and is often seen in the form of a mild epidemic.[142,183,214]

The clinical manifestations of herpangina are comparatively mild and of short duration.[183] The initial symptoms consist of a sore throat and various degrees of general malaise - fever, headache, vomiting prostration, or abdominal pain.[183,214] The patient soon develops small vesicles (which quickly rupture to ulcers) on the soft palate, anterior pillars of the fauces and occasionally on the tongue. The ulcers do not tend to be extremely painful although dysphagia may occur.[183]

The vesicles and ulcers have no particular characteristic appearance and resemble other lesions of viral origin; however, their distribution at the back of the mouth, and in particular on the soft palate, is a diagnostic indicator.[214]

The illness may last up to five days with the lesions healing spontaneously and with no after effects. A permanent immunity usually develops quite rapidly.[183] Despite the fact that the virus may be cultured, cytological and serological tests are not routinely undertaken because of the transient nature of the

illness.[142] For the same reason no treatment is necessary.[183]

Conclusions

It would appear that from the preceding discussion several diseases must be considered in the differential diagnosis of cicatricial pemphigoid.

Behçet's and Reiter's Syndromes are easily distinguished when the characteristic symptom complexes are manifested. Viral illnesses may be distinguished most easily from cicatricial pemphigoid by their self-limiting nature. The remaining conditions - pemphigus vulgaris, bullous pemphigoid, bullous lichen planus and erythema multiforme may be more difficult to distinguish from cicatricial pemphigoid. However, a careful history, systematic examination of the lesions (as described) coupled with their histological appearances will greatly aid in differentiation.

IV DIAGNOSIS

1. Clinical Features

2. The Histopathology of Cicatricial Pemphigoid

3. The Immunopathology of Cicatricial Pemphigoid

IV DIAGNOSIS

Introduction

Cicatricial pemphigoid may be best defined as a relatively rare, chronic, vesiculo-bullous disease which primarily affects the mucous membranes of the oral cavity and conjunctiva.(138) Despite this diagnostically important predeliction for the mouth and eyes, other mucosal surfaces may often be involved by the disease process. The mucous membranes of the nose, larynx, pharynx, anus and genitalia may demonstrate lesions at any time during the course of the disease. Rather less frequently the skin itself may become affected, but only reportedly in between one-quarter and one-third of all cases.(15)

The bullae of cicatricial pemphigoid characteristically form sub-epithelially: that is, a fluid filled cleft develops between the epithelial basement membrane and the underlying connective tissue. It is now also believed that cicatricial pemphigoid is a disease of auto-immune aetiology in which an as yet undetermined component of the epithelial basement membrane zone becomes antigenic and auto-antibody is stimulated. In a proportion of cases binding of either immunoglobulins or complement or both may be demonstrated at the basement membrane zone by direct immunofluorescent examination.(17) Circulating antibodies directed towards the basement membrane zone are also occasionally demonstratable in the patient's serum.(54)

Although the cutaneous lesions of cicatricial pemphigoid seldom heal with scarring, a lamentable feature of the disease is the tendency for the recurring mucosal lesions to form scars on healing. This is most unfortunate because in the case of conjunctival involvement scarring and epithelialization may culminate in blindness from corneal opacification and destruction.

Because bullae by themselves have no particular macroscopical structural features of diagnostic value and also because bullae are only occasionally observed on the oral mucosa (due to the modifying influences of heat, moisture, trauma, and secondary infection) the diagnosis of cicatricial pemphigoid is at times quite challenging.

It is entirely possible to arrive at a diagnosis by following a simple yet usually effective scheme of screening procedures which are admirably suitable to most mucosal diseases. Of prime consideration is a thorough examination of the patient. Included should be a careful record of the patient's description of the natural history of the lesions as well as a systematic examination of any lesions present. In the majority of cases perhaps the single most important diagnostic procedure is the taking of a biopsy. Examination of the tissue by light and electron microscopy (if available) is usually sufficient to confirm a diagnosis of cicatricial pemphigoid. The use of immunofluorescent tests also serves to aid in the confirmation of a diagnosis of cicatricial pemphigoid.

It is the purpose of the following section to elucidate the clinical, histopathological, and immunopathological features of

cicatricial pemphigoid.

1. Clinical Features

As has been stated, the non-specific appearance of the vesicles and ruptured bullae of cicatricial pemphigoid may make diagnosis a difficult task.

Apart from the characteristic occurrence of lesions in the mouth and eyes and occasionally on the skin, other factors which are easily observed clinically may play an important role in elucidating a diagnosis. Features such as the age and sex of a patient may be significant. Also, the careful and close examination of an individual bulla may help demonstrate findings which are significant in making a definitive diagnosis of cicatricial pemphigoid.

Unfortunately, there are a number of factors which may tend to delay the diagnosis of cicatricial pemphigoid, particularly in its early stages:

(a) In the early phase of the disease process it is not unusual to observe short periods of spontaneous remission.

(b) The initial lesions often have a rather non-specific appearance.

(c) Vesicles and bullae (particularly those occurring in the oral cavity) tend to remain intact only for a very brief period of time.

(d) The initial lesions may often be restricted to only a small area and it may be years before other sites become affected.

(e) Cicatricial pemphigoid is a rare condition and only the very alert clinician may make the diagnosis early in its progress.

It is these five factors which primarily and often effectively hinder an early correct diagnosis and also may be responsible for the disease being inadequately treated for long periods.

Before discussing, individually, the important clinical features, it is essential to understand the reasons cicatricial pemphigoid is of significance to dental surgeons:

(a) The oral mucosa may be the initial site in which lesions develop. Hence a patient may first consult a dental surgeon.

(b) The oral mucosa is eventually involved in 100 percent of patients.

(c) One of the most striking and often initial signs of the disease in the dentate patient is the development of a desquamative gingivitis.

(d) Patients who are affected by this disease will require meticulous oral hygiene care and rehabilitation for the remainder of their lives.

(e) In almost all instances the clinical diagnosis should be confirmed by the biopsy and histopathological examination of a suitable lesion - and this biopsy is often taken from the oral mucosa.

(i) Age, Sex and Race

In so far as the age and sex of patients with cicatricial pemphigoid are concerned, certain characteristic findings have been well documented. In broad terms it may be stated that cicatricial pemphigoid generally affects elderly people, a significant number of whom are female.[8,60,67,124,143]

The first large study of cicatricial pemphigoid was undertaken by Lever.[116] He reported thirty such cases. Of these thirty patients, eleven were male and nineteen were female. Their ages ranged from 30 to 84 years but Lever points out that most patients are beyond the age of 60 years at the onset of the disease, this being the average age of the patients in his series.

The study of Shklar and McCarthy[187] was based upon eighty-five patients with cicatricial pemphigoid. Of this large series of patients, seventy-three were female and twelve were male. The ages of these patients ranged from 23 to 75 years with the highest incidence occurring in the 51 to 60 age group. This is the largest study of patients with cicatricial pemphigoid undertaken to date.

The author has reported on a group of fourteen patients with cicatricial pemphigoid.[138] The ages of these patients ranged from 18 to 68 years at the time of reported onset of the disease. The average age of these patients was 56 years. Nine of the patients were female and five were male.

From a review of the literature it is quite apparent that the peak incidence of cicatricial pemphigoid occurs in the 51 to 60 year age group.[132] It is also notable that the number of females with the disease predominates usually in the ratio of

2:1,[14,67,138] or even as high as 3:1.[96] There has been no explanation forthcoming to account for these characteristic findings as regards the age and sex of patients with cicatricial pemphigoid.

Although cicatricial pemphigoid rarely occurs before the age of 40, several well documented cases have been reported in patients in their mid-twenties and younger. Shklar and McCarthy[187] reported two patients who were in their mid-twenties at the onset of their disease. The author[138] has reported a patient who was 18 years old at the time of onset of her disease, as have Worsaae and Dabelsteen.[222] Jolliffe and Sim-Davis[96] described a case of cicatricial pemphigoid affecting a 13 year old girl. Perhaps the youngest patient found to be suffering from cicatricial pemphigoid is one reported by Rogers and Painter.[167] In this case the patient was a 4 year old female child.

Worsaae and Dabelsteen[222] have suggested that the chronic nature of cicatricial pemphigoid, combined with the sparse initial symptomatology like that presented in their report, might delay the establishment of a diagnosis and therefore be one of the reasons for the relatively small number of "young patients suffering from the condition".

Perhaps it would be more accurate to say that the latter part of their suggestion should have read ".....patients being diagnosed as suffering from the condition". Certainly, as has been stated previously, the chronic nature and initial sparse symptomatology of cicatricial pemphigoid will delay its diagnosis in patients of any age. It cannot be assumed that young patients

will have fewer symptoms - in fact the case reported by Jolliffe and Sim-Davis[96] and the youngest patient in the series reported by the author[138] both had severe, wide-spread progressive lesions.

It would appear more likely, therefore, that a breakdown in autoimmune surveillance in association with advancing years may be a more satisfactory means of explaining the propensity for cicatricial pemphigoid to affect elderly patients and the unlikely chance of very young patients developing the disease.

Unlike pemphigus vulgaris in which a significant percentage of patients affected are Jewish, cicatricial pemphigoid has shown no such predilection for race or nationality.[8,14,64,124,138]

(ii) Oral Manifestations of Cicatricial Pemphigoid

The oral mucous membrane is rarely, if ever, spared in any case of cicatricial pemphigoid.[186] It is also the most frequent site of onset of the disease and may remain the only area of activity for several years.[116,203] In general there are three basic types of lesion which may occur on the oral mucosa:. a desquamative form of gingivitis, vesiculation and bulla formation, and ulceration (representing the remnants of collapsed bullae). Due to the protracted course taken by cicatricial pemphigoid and the slow healing of the lesions, various stages of the disease may be present simultaneously.[8]

There are several features of the oral lesions of cicatricial pemphigoid which are distinctive.[8,125,186] The lesions develop

quite slowly, with perhaps only one or two areas being initially involved: very often weeks pass before further lesions are observed. The individual lesions are also initially quite small and clear-cut in nature.

The commonest initial site of involvement in the dentate patient is the gingivae and the lesions take the form of a desquamative gingivitis.

(ii)(a) Desquamative Gingivitis

In 1960, McCarthy, McCarthy and Shklar[123] expressed considerable doubt as to the specificity of the lesions of gingivitis which was characterized by an intense erythema and desquamation. These authors wondered whether this curious condition was a specific clinical entity or merely a gingival manifestation of a variety of systemic distrubances with differing aetiologies.

Despite the occasional insistance in the modern literature that desquamative gingivitis is a disease entity that should be classified separately from other conditions,[63] the weight of present-day opinion would seem to favour the belief that desquamative gingivitis is a reaction pattern rather than a disease sui generis.[37,123,170,214]

Desquamative gingivitis is a common clinical manifestation of a number of entities: dermatoses, hormonal factors, irritational factors and idiopathic factors.[9,37,147,214] These dermatoses include cicatricial pemphigoid, pemphigus vulgaris, lichen planus, and occasionally bullous pemphigoid. Thorough clinical evaluation, including examination of the mucous membranes and skin, may show

evidence of the diseases mentioned above. Histopathological examination of a routine biopsy specimen of the involved mucosa as well as immunological studies may serve to confirm a diagnosis.[170,214]

Clinically, the classical appearance of desquamative gingivitis is characterized by a shedding of the superficial gingival epithelium to expose a raw and haemorrhagic base of connective tissue. As has been stated, this gingival involvement is a most characteristic and striking feature of cicatricial pemphigoid. Desquamative gingivitis is found in all cases of cicatricial pemphigoid where teeth are present.[132,187]

In desquamative gingivitis the gingiva appears both deep red and shiny.[132,187,214](Fig.IV.1) The lesions involve the gingival margin, the attached gingiva, but would appear not to extend into the loosely attached alveolar mucosa. The intensity of the erythema is variable and the involvement may be diffuse or may appear as patchy zones of varying degrees of redness.[187] The interdental papillae may also appear to be somewhat swollen.[214](Fig.IV.2) Actual desquamation may be associated with a yellowish-white surface necrotic slough appearing particularly in areas of notable erythema.(Fig.IV.3) Desquamation of the gingival surface may also occur upon palpation of the tissues with a finger or an instrument - thus confirming the positive Koebner phenomenon associated with cicatricial pemphigoid. Vesiculation may also occur on the gingiva, and rupture of these vesicles results in irregularly shaped ulcerative areas.

Fig.IV.1. Desquamative gingivitis. The gingiva is deeply erythematous and there are areas of necrotic slough. (Patient 12. Table V)

Fig.IV.2. Desquamative gingivitis. Many of the gingival papillae are swollen and erythematous. (Patient 6 Table V)

Fig.IV.3. Desquamative gingivitis. Areas of desquamation on the mandibular gingiva are covered with necrotic slough. (Patient 6. Table V)

Fig.IV.4. Desquamative gingivitis. A very low level of oral hygiene has led to a superimposed periodontitis. (Patient 1. Table V)

In true desquamative gingivitis the periodontal ligament is not directly involved.(214) However, because the lesions of desquamative gingivitis may cause great discomfort when eating and cleaning the teeth, the vast majority of patients will show alveolar bone loss due to secondary disease consequent upon the difficulty in maintaining an adequate level of oral hygiene.(Fig.IV.4)

Another characteristic feature of desquamative gingivitis is its tendency to heal remarkably slowly, so much so that quite notable erythema may remain extant for months or even years despite the suppression of the other lesions associated with cicatricial pemphigoid. The reasons for this anomalous situation remain unclear.

The histopathological and immunopathological patterns of biopsy specimens taken from areas of desquamative gingivitis in patients with cicatricial pemphigoid are in keeping with those of biopsy specimens taken from other mucosal sites. These patterns will be discussed in a later section.

(ii)(b) Vesiculation and Bulla Formation

Intact oral vesicles, although not often seen, are still more commonly observed in cicatricial pemphigoid than in other vesiculobullous diseases because their subepithelial nature provides somewhat more resistance to mechanical trauma than the intraepithelial lesions in diseases such as pemphigus vulgaris and erythema multiforme.(132)

Although the other regions of the oral cavity are less commonly involved than the gingiva, the lesions tend more to be

vesiculobullous in nature rather than desquamative.[187] The oral lesions will generally start as vesicles or bullae with a marginal zone of erythema. A diffuse reddening of the mucosa may be noted before the vesicles actually make their appearance.[125,126]

Fresh unruptured vesicles and bullae, as has been stated, are rarely observed, but a recently collapsed vesicle presents a fairly characteristic lesion, with the thick, white, partially denuded epithelium resting on a bright, erythematous, eroded base.[125] The vesicles of cicatricial pemphigoid also tend to coalesce rather than enlarging by lateral spread (as in pemphigus vulgaris).

As has been stated previously, to the untrained eye bullae by themselves may have no macroscopical structural features of any diagnostic importance. Despite the generally indistinct character of most intra-oral bullae and their only occasionally being observed intact on the oral mucosa, the investigator who is familiar with and trained in oral pathology may be able to distinguish small differences between bullae of different diseases which are sufficiently significant as to suggest a diagnosis.

It is most important to determine that the lesion being observed is in fact a bulla. Often lesions of the oral mucosa are described as bullae that are in fact not bullae at all. Beads of mucus at the mouths of excretory ducts of the minor salivary glands, oedematous fungiform papillae and shallow minute erosions or ulcers covered with fibrinous sloughs may all mimic very closely the appearance of bullae.

When an intra-oral bulla is observed careful examination may assist greatly in determing whether it is indeed a manifestation of cicatricial pemphigoid. A tentative diagnosis of cicatricial pemphigoid may be made by a clinical examination of an intact oral bulla under the following headings.[140]

Location of the Bullae

Actual vesicles and bullae most often occur on the mucosa of the hard and soft palates as well as the buccal mucosa.[44,67,132,187,214](Figs.IV.5,6,7) The lateral and ventral surfaces of the tongue also occasionally show areas of vesiculation and bullae formation.[138] In the dentate patient the lesions that affect the gingivae tend to be desquamative rather than vesicular in nature, although some authors claim that vesicles may sometimes be seen.[44,187]

In the edentulous patient where a prosthesis undergoes significant movement, vesicles may frequently develop on the mucosa beneath the denture base and its peripheries.[132,138](Fig.IV.8)

Type of Bullae

Due to the subepithelial site of vesiculation, the bullae of cicatricial pemphigoid are characteristically thick-roofed.[187,214] They are also relatively tense.[67] Although the vesicle fluid is usually clear,[187] it is not unknown for a "blood filled" bulla to be observed.[138](Figs.IV.5&7)

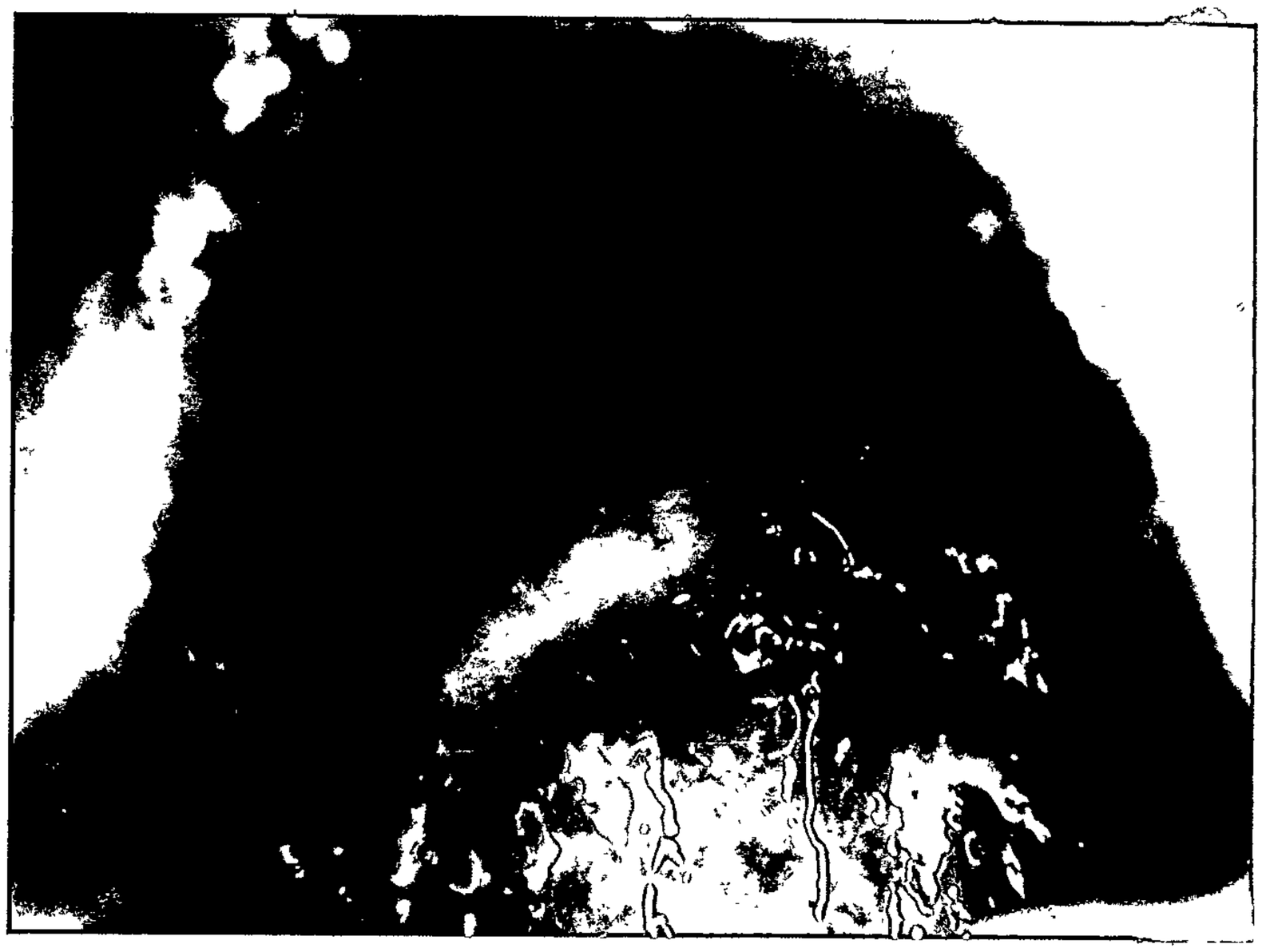

Fig.IV.5. A single,small,clear vesicle at the midline of the junction of the hard and soft palates.(Patient 5. Table V)

Fig.IV.6. Multiple small vesicles on the right soft palate. (Patient 4. Table V)

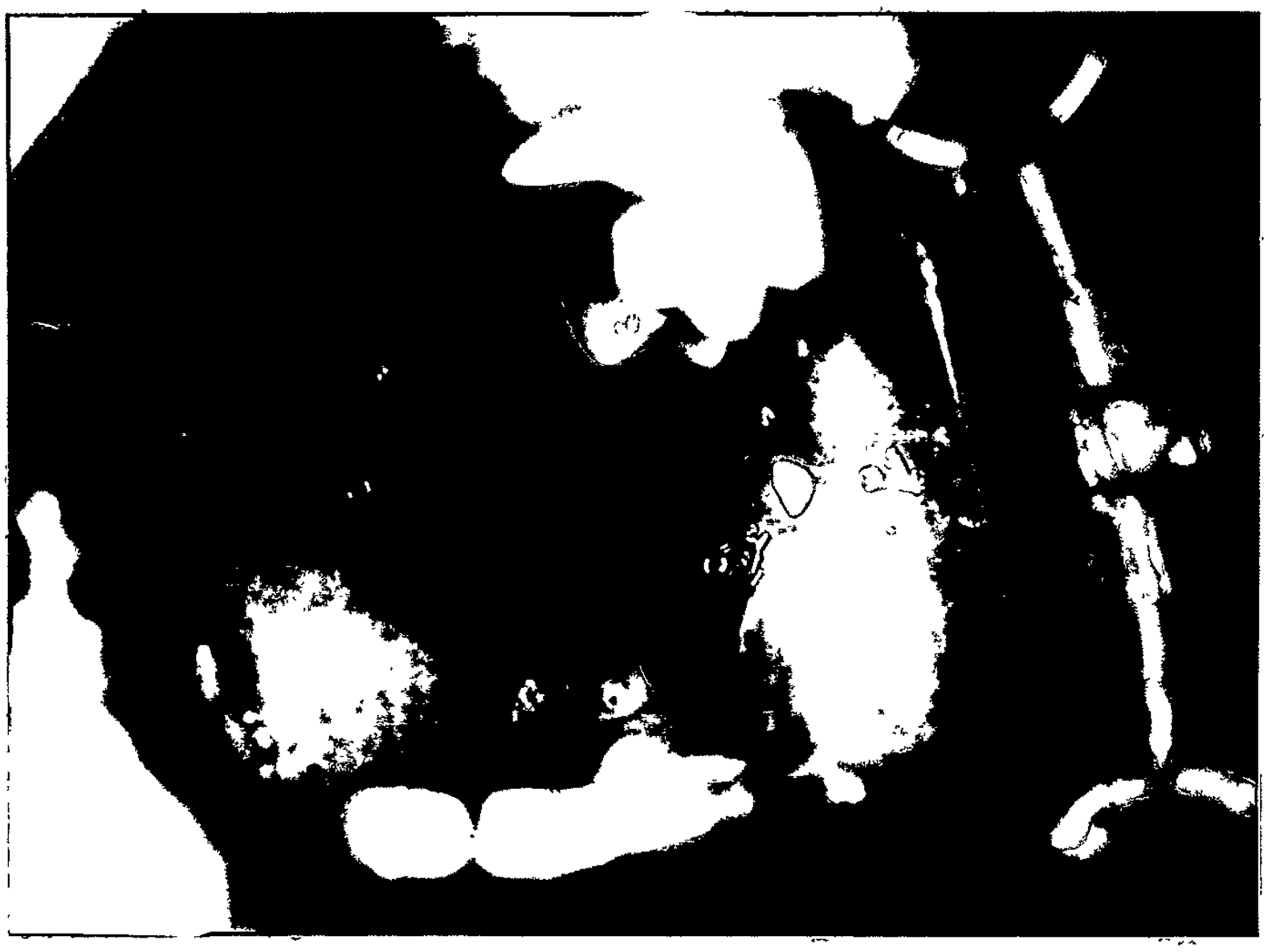

Fig. IV.7. A blood filled bulla on the buccal mucosa. (Patient 12. Table V)

Fig.IV.8. A blood filled bulla on the retromolar mucosa associated with a full mandibular denture. (Patient 11. Table V)

Rapidity of Development and Rupture

The bullae of cicatricial pemphigoid generally develop fairly rapidly.[187] Their subepithelial nature provides somewhat more resistance to mechanical trauma than the intraepithelial lesions of pemphigus.[132] Hence the bullae may often last as long as 48 to 72 hours before rupturing.[67,124,132,187] It would appear, however, that the location of the bulla on the oral mucous membrane and the subsequent degree of trauma it is exposed to, may determine the number of hours it remains intact.

Pressure with the Finger on Bullae

An interesting phenomenom which occurs in pemphigus vulgaris is the tendancy for a bulla to spread laterally following pressure by means of a finger pressed on its roof.[140] This is due to the loss of attachment of the prickle cell layer. One might expect that due to the loss of attachment of the epithelium to the connective tissue in the bulla of cicatricial pemphigoid a similar ability to spread such a lesion laterally might occur. This occurrence has not been reported.

Forman and Nally[65] have, however, been able to clinically demonstrate the loss of adherence of the epithelium to the corium by the insertion of a blunt, flat probe under the epithelial edge of a bulla. The probe could be passed under the epithelium without resistance, and when in position, a side to side movement of the probe would detach the epithelium and subsequently allow its elevation.

The Tissue Immediately Surrounding the Bullae

The vesicular and bullous lesions of cicatricial pemphigoid as they affect the oral mucous membrane tend to be fairly striking in their clear-cut nature.(125) The lesions are also seen to have an erythematous peripheral area.(125,138,140,187) The ulcers which form following the rupture of the bullae have characteristic regular, clear-cut margins in contrast to the more ragged-appearing ulcers of pemphigus vulgaris.(44)

Nikolsky's Sign and Koebner's Phenomenon

It is important to define these two terms as they have been used synonymously in some circumstances.

Nikolsky's sign refers to a slipping or peeling of the epithelium at the epithelial-connective tissue junction under slight lateral pressure.(183) As has been stated, pressure on the roof of a bulla of cicatricial pemphigoid does not appear to cause it to spread laterally. However, as demonstrated by the "probe test" of Forman and Nally,(65) it is possible to instrument the lateral spread of a bulla of cicatricial pemphigoid.

The Koebner phenomenon (isomorphous provocative reaction) refers to the appearance of bullae at sites of trauma.(170) The commonest source of oral trauma in edentulous patients suffering from cicatricial pemphigoid is a dental prosthesis. Lesions are commonly observed beneath dentures and in relationship to their peripheries.(126,132,138,207) Vesicle and bulla formation has also been seen in skin graft donor sites in patients with cicatricial pemphigoid in whom lesions could be induced

experimentally by traumatizing apparently normal tissue.

Scar Formation

It is quite possible that as the lesions of cicatricial pemphigoid heal they will cause scarring to occur.[44] This, however, occurs less commonly in the mouth and more often in the eyes.[14,186] The areas of the oral cavity most frequently affected by scarring are the mucobuccal folds (particularly in association with denture peripheries) and about the uvula and tonsillar areas. (Fig.IV.9)

(ii)(c) Ulceration

Oral ulceration in varying degrees is present in virtually all patients with cicatricial pemphigoid and represents the remnants of collapsed bullae.[138] In the strictest sense these lesions are not in fact ulcers. An ulcer is a lesion in which there is loss of continuity of the epithelial surface, with the underlying connective tissue being exposed, and as such tends to be cratered and show an inflamed base. The remnant of a collapsed bulla, however, tends to be raised above the surface of the surrounding intact epithelium and has a surface constituted from degenerating epithelium, which once formed the roof of the collapsed bulla. (Fig.IV.10) For want of a better term, however, these lesions will be referred to as ulcers.

The oral bullae of cicatricial pemphigoid usually break down within two to three days to leave secondary ulceration.[44,67,79] As has been stated, a recently collapsed bulla presents a fairly

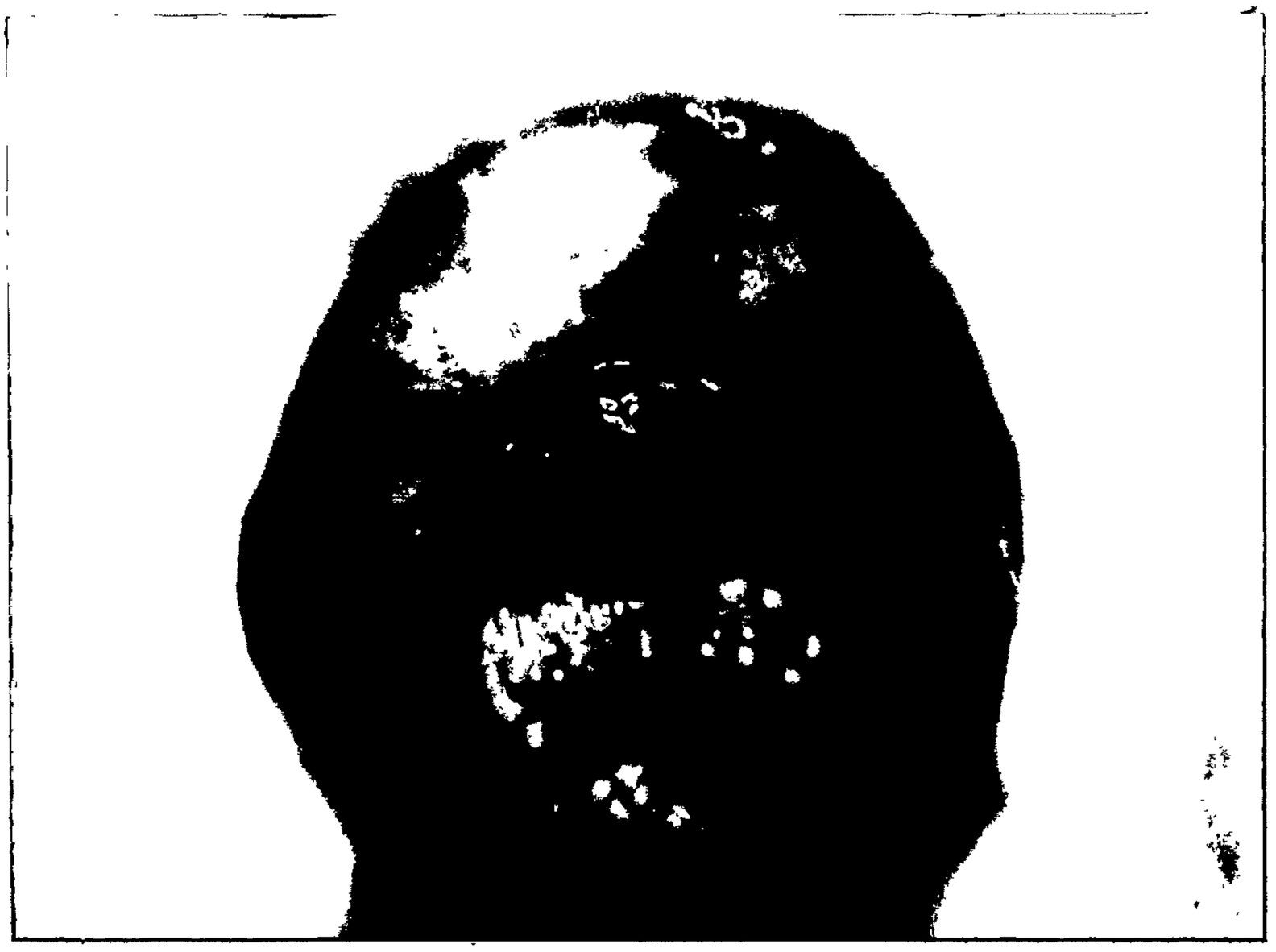

Fig.IV.9. Scarring has been so severe as to cause retraction and adhesion of the uvula to the soft palate. (Patient 13. TableV)

Fig.IV.10. The remnant of a collapsed bulla. The degenerating epithelial roof has been peeled back to expose the connective tissue base. (Patient 9. Table V)

characteristic appearance with the thick yellow-white, partially denuded epithelium resting on a bright, erythematous and eroded base of connective tissue.[25,125,126]

When the condition is most active these ulcerative lesions coalesce to involve extensive areas of the oral mucosa, following the development of subsequent crops of vesicles.[79,116](Figs.IV.11&12) The large denuded areas in the mouth seen in cicatricial pemphigoid have several characteristic features, particularly when compared to similar types of lesions in pemphigus vulgaris.[44,116,125,126,186] Since they form by coalescence of subsequently appearing and rupturing bullae rather than by peripheral enlargement of existing lesions, they usually do not show shreds of epithelium at the border (i.e. a ragged appearance) and thus appear cleaner.(Fig.IV.13) The areas of ulceration also tend not to bleed easily and cause little pain. Furthermore, the vermillion border of the lips is only very rarely involved.(Fig.IV.14)

It is surprising, despite the sometimes extensive areas of oral mucosal ulceration, that pain is not a more significant feature of cicatricial pemphigoid. An explanation for this apparent incongruity may lie in the fact that the ulcerated areas are not ulcers in the true sense and have a degenerating epithelial covering protecting the underlying sensitive connective tissue. This explanation is borne out by the observation that gingival lesions are quite painful and it is in this area that true desquamation to expose the underlying connective tissue has occurred.

Fig.IV.11. Extensive ulceration; a similar area of ulceration affected the right cheek. (Patient 6. Table V)

Fig.IV.12. Recurrent vesiculation at the junction of the hard and soft palates has caused extensive ulceration. (Patient 14. Table V)

Fig.IV.13. Three ulcers with well demarcated peripheries on the tip of the tongue. (Patient 9. Table V)

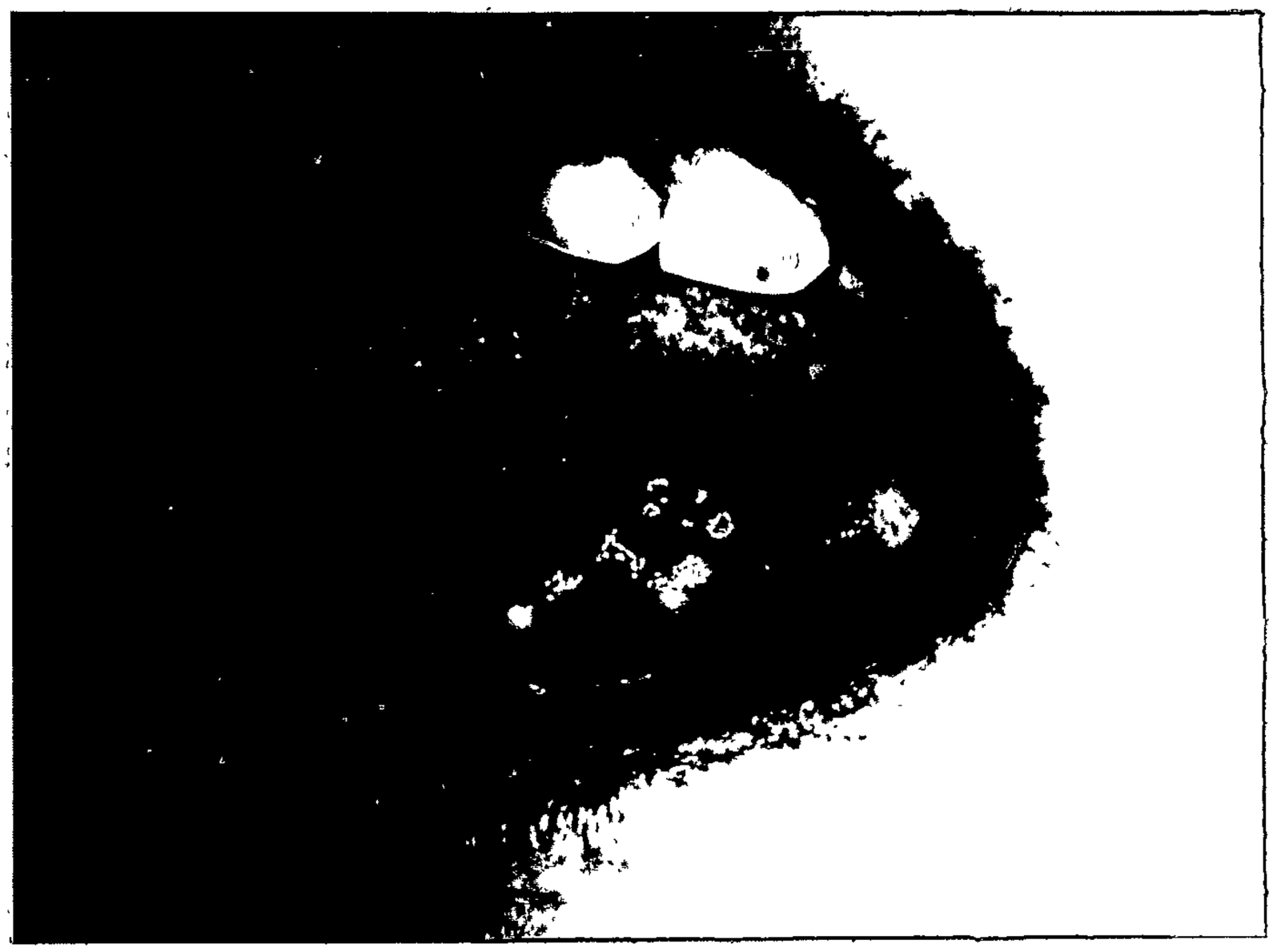

Fig.IV.14. An unusual finding. The suggestion of ulceration extending onto the vermillion of the upper and lower lips. (Patient 6. Table V)

When the ulcerative lesions (other than those of the gingiva) do become painful it is perhaps due to secondary bacterial and fungal involvement. This infection is non-specific and merely represents the normal oral flora complicating the ulcerative lesions.[187] The organisms of Candida albicans would seem to play a part in this secondary infection and subsequent discomfort. Significant infection of the oral ulcerations with pathogenic organisms does not occur due to the natural antibacterial influences in the mouth, and any suppuration is limited to the ulcer floor.[187]

The duration of ulcerative lesions is quite variable, some healing in a few weeks, and others persisting for long periods due to the concurrent development of further vesicles.[187]

(iii) Ocular Manifestations of Cicatricial Pemphigoid

In cicatricial pemphigoid the conjunctiva is the prime site of ocular involvement.[10] In most cases in which the disease process affects the ocular apparatus the conjunctival involvement is the most conspicuous, severe and disabling of all the lesions of cicatricial pemphigoid, for which reason the disease became first known as ocular pemphigus or pemphigus conjunctivae.[116,125,201] Eye lesions represent the most serious complication of cicatricial pemphigoid, as quite considerable loss of vision may result from the effects of scarring.[138,186]

Conjunctival involvement occurs next in frequency to oral lesions and is also the next most common site of onset.[14,132,138] In the three largest series of cases, the conjunctiva was involved 61 percent,[187] 76 percent[76] and 80 percent[116] of the time.

Involvement of the eyes is usually bilateral(Fig.IV.15) but it may be unilateral.[14,132] Hardy and his co-workers[76] found that in 87 percent of their cases both eyes were involved. Conjunctival involvement in each eye is usually not of similar severity and the involvement in one eye may precede the other sometimes by as long as several years.[10,76](Fig.IV.15)

The ocular involvement usually consists of a relentless conjunctivitis with the more serious problems of symblepharon developing superimposed upon the conjunctivitis as the disease progresses.[132] An unyielding conjunctivitis with varying degrees of scarring is present in some 75 percent of cases.[14] Blindness is reported to occur in up to 20 percent of cases despite the efforts of treatment.[14,138]

The early clinically detectable involvement is usually slow and insidious. At first the appearance is that of a simple catarrhal conjunctivitis and may often go mis-diagnosed until more advanced lesions appear.[116,125]

At the onset the symptoms of ocular involvement are vague and non-specific.(Fig.IV.16) They generally consist of an irritating, chronic, non-specific conjunctivitis with persistent burning and smarting pain, excessive tearing, a foreign body sensation and sometimes an early photophobia.[39,76,105,182] Remissions and exacerbations are quite common and some blurring of vision may occur.

Later, the conjunctival infection becomes chronic and there is a progressive but slow reduction in lacrimation, and the discharge tends to become a thick, ropy, mucous, sometimes foamy

Fig.IV.15. Bilateral ocular involvement: the right eye being affected for some time before the left. (Patient 1. Table V)

Fig.IV.16. Mild non-specific conjunctivitis producing some granulation tissue and loss of eyelashes from the lower lid. (Patient 4. Table V)

secretion.[39,76,182] This discharge in many cases becomes mucopurulent owing to secondary infection.

The formation of vesicles is not obvious, nor is it a universal finding.[39,105,116,187] Their rarity is attributable to their delicate nature and the ease with which they rupture.[88] Despite their apparent rarity, Baum[10] reports that they have been seen in 25 percent of cases, and indeed Bedell[18] states that they are the earliest sign of the ocular lesions of cicatricial pemphigoid.

The bullae are described as being delicate short-lived, thin-walled and smooth-surfaced, being somewhat greyish.[18] They may arise most often on the palpebral conjunctiva, generally in the lower cul-de-sac, although they may also be found on the cornea.[39] They tend to sprout from a beefy-red base of macerated epithelium and may be single or multiple, isolated or confluent, and varying in size from a few millimetres to one centimetre or more in diameter.[18] The fragility of the bullae renders them liable to burst, thus leaving a reddish ulcerated base covered by a grey macerated epithelium, which when desquamated is not replaced by fresh epithelium but rather by fibrous cicatricial tissue.[105]

Each recrudescence of the disease with vesiculation and ulceration is followed by cicatrisation and sub-mucous shrinkage.[105] The disease process proceeds inexorably and in the course of time small fibrous adhesions develop between the palpebral and bulbar conjunctivae and also between the inferior and superior palpebral conjunctivae.[187] Involvement of the inferior cul-de-sac is

generally more marked than is that of the superior.[76,138] Later there is formation of symblephara which eventually obliterates the entire cul-de-sac. As the number and extent of adhesions between bulbar and palpebral conjunctivae increase, both eyelids may become firmly attached to the globe of the eye, inhibiting greatly its movement.[116] Adhesions of the edges of the eyelids (ankyloblepharon) may also occur and result in narrowing or even obliteration of the palpebral fissure.[116,187] (Fig.IV.17)

Symblepharon formation also leads to the development of cicatricial entropion and to trichiasis.[10] This inversion of the margins of the eyelids, followed by trichiasis (irritation of the globe by friction), eventually leads to corneal damage.

In cicatricial pemphigoid, corneal involvement occurs secondarily to the conjunctival lesions.[10] Several different processes may lead to corneal damage. Firstly, trichiasis may cause corneal ulceration and opacities.[116] Secondly, scar constricture of the ductal ostia from the lacrimal gland may lead to an actually, dry, tearless eye.[132] Scar constricture of the canicular ostia of the nasolacrimal ducts may also produce frank epiphora in the earlier phases of inflammation and cicatrisation. This xerosis will lead to degeneration of the cornea. A decrease in the normal tear film integrity with loss of wetting action due to reduced mucus production secondary to goblet cell destruction also contributes to the pathological condition of the cornea.[10] Thirdly, pannus formation, consisting of a gradual growth of vascular and connective tissue from the conjunctiva over the cornea may occur.[116]

Fig.IV.17. Severe ocular involvement. The eyelashes have been lost. Symblepharon formation has led to marked entropion of both eyelids. Ankyloblepharon has caused great narrowing of the palpebral fissure.

(Patient 1. Table V)

Localized conjunctival lesions lead to circumscribed cicatrisations, while the reduced tear secretion effects a universal dessication, accentuated by the frequent presence of a certain degree of lagophthalmos (a condition in which the eyelids do not close due to symblephara) with a consequent increased evaporation and continuous exposure of the eye.[105] Both the conjunctiva and the cornea will gradually become dry, causing destruction of normal corneal tissue, corneal inflammation and neo-vascularisation.[10] This combination of factors eventually causes the eye surface to have a parchment-like opaque appearance due to the proliferation of granulation tissue and connective tissue from the conjunctival sacs. This opaque, horny membrane has the same surface appearance as does the epidermal surface of the skin.[116]

Thus the sequellae of conjunctival involvement in cicatricial pemphigoid may be serious. Pain and burning are quite severe, the patient has difficulty in opening his eyes, the cul-de-sac becomes obliterated, and the cornea becomes scarred and opaque. Blindness is surely inevitable if the condition remains untreated. The inflammation of the conjunctivae may become arrrested spontaneously at any time, and because the disease generally has its onset later in life, many patients may be spared the ultimate complication of blindness.

(iv) <u>The Dermal Manifestations of Cicatricial Pemphigoid</u>

Although cicatricial pemphigoid is a disease which characteristically affects the mucous membranes, it is not uncommon

for a percentage of these patients to develop cutaneous lesions directly attributable to the disease process.

Skin lesions, like those of the nose, pharynx and larynx, seem to be more prevalent than the early reports indicated. It would appear that somewhere between 20 percent to 50 percent of patients with cicatricial pemphigoid will either have dermal lesions as part of their initial presenting syndrome or will develop such lesions sometime during the course of their disease.[14,79,125,126,132,138] There are perhaps two possible explanations as regards the lower percentage of cases reported with dermal lesions. In more recent times diagnosis and institution of therapy have occurred at an earlier phase in the disease process, thus reducing the possibility that skin lesions will develop.[186] In the earlier literature, however, it is possible that many cases with skin lesions were reported under the diagnosis of pemphigus.[114]

In the three largest series of cases of cicatricial pemphigoid reported to date, the skin was involved 11 percent,[187] 23 percent,[76] and 43 percent[116] of the time.

Lever[116] has described two types of cutaneous lesions. One type of lesion consists of a recurring eruption of discrete bullae, usually limited in extent and healing without atrophy. The most commonly affected areas are the penis and the legs. The other type of lesion consists of areas of erythema, usually few in number with a predilection for the face and scalp.(Figs.IV.18&19) Within these areas of erythema, flaccid bullae may occasionally erupt at intervals and leave denuded areas. After a considerable

Fig.IV.18. A chronic area of erythema with a periphery of some slight dermal atrophy. (Patient 1 Table V)

Fig.IV.19. Several chronic erythematous plaques with some dermal atrophy on the temporal scalp. (Patient 9. Table V)

period of time these areas heal with smooth and atrophic scarring, or become ulcerated.(Fig.IV.20) Such ulceration is superficial, moist, and with little evidence of epithelialization.[194] The first type of dermal lesion, described by Lever,[116] is a more generalized eruption of scattered bullae whereas the second type of lesion (recurrent cicatricial plaques) occur most commonly near mucosal surfaces and on the scalp.[161] Several authors[125,126,186] have expressed the opinion that the appearance of dermal lesions usually accompanies a general exacerbation of the mucosal disease and that they respond to steroid therapy or subside spontaneously during a remission of the mucosal lesions.

A good deal less than 50 percent of the dermal lesions of cicatricial pemphigoid consist of that type which will heal with atrophic scarring.[132] Up until the report by Lever[113] of three cases of pemphigus conjunctivae (as he then termed the disease) with scarring of the skin, there had only been a handful of cases reported in the literature.

The first case of cicatricial pemphigoid associated with cutaneous scarring was reported by Morris and Roberts[141] in 1889. They described a woman of 60 years of age who had oral lesions and cicatricial ocular lesions as well as cutaneous lesions.

> ".....the skin of almost every part of the body
> was marked by scars of various ages and appearance."
> ".....both cheeks was converted into glossy,
> scarlike tissue of a mottled purplish colour."

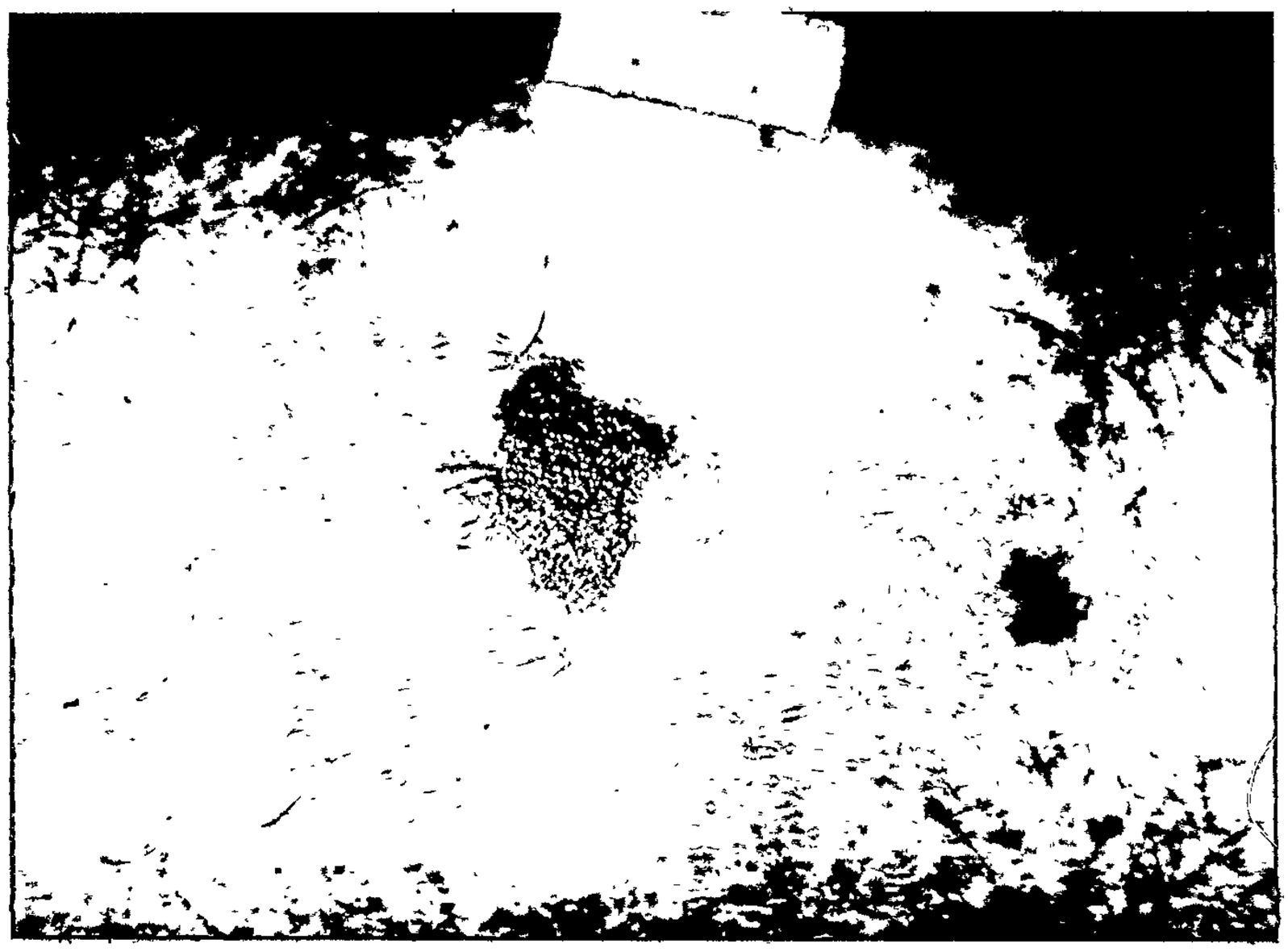

Fig.IV.20. A chronic ulcer on the forearm which reportedly became blistered on occasions. Scarring and atrophy have occurred peripherally.(Patient 14. Table V)

Lever[114] has hypothesized that the scarring of the skin in cicatricial pemphigoid may be caused in two ways. Either the continuous appearance of new bullae within a circumscribed area results in a gradually developing atrophy of the skin, or superficial ulcerations rather than erosions develop after the bullae break. Frequently, however, he believed that there was a combination of these two factors; continuous appearance of bullae in one area leading to ulceration and subsequent scarring.

(iv)(a) Localized Chronic Pemphigoid (Brunsting-Perry Type)

The concept that circumscribed blistering plaques with scarring, located about the head and neck, might be a part of the syndrome of cicatricial pemphigoid was first developed by Lever.[113]

In 1957 Brunsting and Perry[30] described seven patients with what they believed was a unique form of cicatricial pemphigoid. All of the patients, except for one, were males and all were middle-aged or older. These patients were observed over a period of several years to have an eruption of an identical pattern. This was characterized by grouped, pruritic vesicles or more circumscribed plaques about the skin of the head and neck, which extended through a succession of annoying exacerbations and culminated eventually in scarring of the affected sites. Usually one primary plaque evolved and slowly enlarged with the formation of small bullae at the advancing margin. In only one patient was the oral and conjunctival mucosa affected, albeit transiently and without scarring. The general health of the patients was

unimpaired and the process was considered essentially benign. The histopathological appearance of these cutaneous lesions showed localization of the bullae at the subepidermal level.

Since the report by Brunsting and Perry,[30] most authorities consider this condition to be a distinct clinical variant of cicatricial pemphigoid with its recognition as such being quite important as these patients seem to be spared the considerable morbidity associated with classical cicatricial pemphigoid.[14,94,146,161] In more recent times this particular variant has become known as localized chronic pemphigoid.

Localized chronic pemphigoid is a rare, chronic bullous disease which probably occurs in two distinct forms.[161] The first type corresponds to that described initially by Brunsting and Perry[30] in which scarring bullous plaques occur on sun-exposed areas, especially on the head and neck, which predominates in males and is resistant to therapeutic measures. The second type consists of cases in which lesions are more bullous, being less cicatricial and less plaque-like, usually occurring pretibially in women, and often can be controlled by topical medicaments. As has been stated, localized chronic pemphigoid appears to be a variant of cicatricial pemphigoid without involvement of the mucosae, and running a protracted course.[146,218]

It is interesting to note that the lesions in patients with localized chronic pemphigoid are localized to relatively sun-exposed areas. As discussed in a later section, the studies of Cram and Fukuyama[48] have shown that the characteristic immunological and histological lesions of pemphigoid can be induced on

the normal skin of bullous pemphigoid patients by ultraviolet light. It may therefore be reasonable to assume that exposure to the sun may contribute to the pathogenesis of lesions on the head, neck and scalp in males and the lower legs in females who suffer from localized chronic pemphigoid.[161]

The clinical, histopathological, and immunological characteristics of localized chronic pemphigoid are such as to suggest a relationship with cicatricial pemphigoid and bullous pemphigoid. The immunological characteristics of localized chronic pemphigoid and its position in the cicatricial pemphigoid-bullous pemphigoid disease spectrum will be discussed in a later section.

(v) Other Mucous Membrane Manifestations of Cicatricial Pemphigoid

Although being somewhat less commonly involved than the oral cavity and the conjunctiva, any of the other so-called orificial mucous membranes may be affected by the lesions of cicatricial pemphigoid. These include the mucous membranes of the nose, larynx, pharynx, oesophagus, genitalia and anus.[14,79,116,132,138]

It is an unfortunate feature of the disease that involvement of these other mucosal surfaces often goes unobserved. This may be due to the mild symptoms produced by the disease or the failure to routinely examine all mucous membrane-lined orifices.[132] This latter reason may well be a function of what type of clinician first examines the patient. However, in the large study made by Hardy and his co-workers,[76] a concerted effort was made to examine the

mucous membranes of nose, pharynx, larynx, oesophagus and rectum.. Their findings that these mucosal areas are involved in a significant percentage of cases should encourage the clinician to thoroughly examine all mucosal tissues.

(v)(a) Nasal Mucosa

In the four largest series of cases of cicatricial pemphigoid the nasal mucosa was involved 38 percent,[76] 8 percent,[187] 40 percent,[116] and 28 percent[158] of the time. The much lower figure of the survey by Shklar and McCarthy[187] is probably due to the fact that the nasal mucosa (as with other non-oral and non-conjunctival mucosal sites) was not routinely examined.

Although vesicles have been observed on the nasal mucosa they are less common than in the mouth.[76] In the nose, active lesions in such a highly vascular tissue frequently cause epistaxis.[76,132,208] A chronic, serosanguineous nasal discharge is also a typical feature of nasal involvement.[14,76,132] These lesions may mimic those of a chronic rhinitis.[116] Examination may reveal diffuse inflammation, circumscribed erosions, atrophy, large areas of crusting, and occasionally fibrous adhesions between neighbouring mucosal surfaces.[116] It was a common finding by Hardy and his co-workers[76] that crusting often led to nasal obstruction which at times required repeated surgical intervention to maintain patency. A similar case was recorded by Thomas[208] in which the severity of the lesions was such as to cause the inferior turbinate to become adherent to the nasal septum, with marked crusting and considerable reduction in nasal

patency. Again it was necessary to intervene surgically to sever adhesions and restore patency of the nostril.

(v)(b) The Larynx

The larynx appears to be affected by lesions of cicatricial pemphigoid at a quite variable frequency. Lever[116] in his series of 30 cases found laryngeal involvement in 47 percent of patients. Hardy and his co-workers[76] in their series demonstrated laryngeal lesions in 30 percent of their cases, whereas Person and Rogers[158] only found 5 percent of their patients with laryngeal involvement. Despite these wide ranging figures the morbidity of laryngeal involvement in cicatricial pemphigoid should not be under-estimated.

Involvement of the larynx may lead to chronic, recurrent soreness and hoarseness, and also to the accumulation of mucus in the throat.[116]

Vesicles are not often seen and the most common lesion found on indirect laryngoscopy are erosions on the epiglottis and arytenoid areas.[76,116] The true vocal chord mucosa is usually spared.[132]

When scarring does occur bands of adhesions may cause laryngeal stenosis, leading to upper airway obstruction. The frequency of this occurrence is fortunately reportedly quite rare although Hardy and his co-workers[76] reported that two of their patients developed life-threatening laryngeal stenosis and one of these required tracheostomy on three separate occasions. Person and Rogers[158] also reported a case of laryngeal stenosis

requiring tracheostomy. The author has also personally observed one female patient who had undergone sub-total laryngectomy due to unrelieved chronic laryngeal stridor.[138]

Due to the possible debilitating effects of laryngeal scarring and stenosis, indirect laryngoscopy should be performed on all patients who complain of symptoms suggesting laryngeal involvement.

(v)(c) Pharynx and Oesophagus

Pharyngeal involvement occurs in a considerable number of patients.[14] Hardy and his co-workers[76] demonstrated 43 percent of their patients as having recurrent lesions. Person and Rogers[158] recorded 46 percent of their patients as having pharyngeal involvement. Approximately one-third of patients will show vesicles and bullae.[76]

The two most frequent pharyngeal complaints are a mild sore throat and difficulty in swallowing.[76,132] Occasionally scarring will lead to stenotic webs of fibrous tissue between the soft palate and the naso-pharynx which may require frequent digital manipulation to destroy adhesions and maintain a nasal airway.[14,76]

Oesophageal involvement is fortunately an infrequent occurrence.[14] Hardy and his co-workers[76] reported an incidence of only 7 percent, Shklar and McCarthy[187] a 2 percent, Lever[116] a 13 percent, and Person and Rogers[158] a 6 percent incidence.

Symptoms of oesophageal involvement are almost always related to the superior portion of the oesophagus, usually at the clavicular level which can be demonstrated by barium swallow.[76,116,132] Loss of weight due to an inability to swallow foods is an expected

sequel.

Patients complain of difficulties in the passage of food after it has been swallowed and usually they can eat only finely ground food and liquids.[116] In some patients, Lever[116] reports that occasionally a bolus of food gets lodged in the oesophagus.

Roentgenographic examination of the oesophagus after barium swallow may reveal several areas of constant narrowing at the site of the strictures.[116] Oesophagoscopy will show diffuse inflammation of the mucosa and web-like adhesions which may cross the lumen of the oesophagus hence dividing it.[64,76,116,137,187] The adhesions are soft and pliable at first and can usually be easily divided by oesophageal dilatation.[14,116] However, later they become fibrous and rigid and resist dislodging, a factor which may become life-threatening.[137]

Minkin, Selinger and Averbach[137] reported a case in which ten separate hospitalizations for oesophageal dilatation were required over a period of two years despite intensive corticosteroid therapy. An unusual case was reported by Foroozan and his co-workers,[66] in which a patient developed such oesophageal involvement that the oesophageal epithelium was sloughed and expelled through the mouth in toto as a hollow membranous cast. Complete reversal to a normal histological picture did not occur, and the total thickness of the oesophageal squamous epithelium remained considerably thinner than that of normal subjects.

Hence early recognition of oesophageal involvement is important because early adhesions can be dislodged and severe

stenoses can thus be prevented. Therefore any patient with cicatricial pemphigoid who complains of dysphagia should have a roentgenographic examination of the oesophagus by means of a barium swallow.

(v)(d) The Genitalia

Genital involvement in both men and women occurs not infrequently.[14] In the study by Hardy and his co-workers,[76] 21 percent of males and 35 percent of females had genital lesions. Shklar and McCarthy[187] reported a frequency of genital lesions of 21 percent with no reference to sex. Lever[116] in his study of 30 patients, found 10 percent of males and 17 percent of females had genital lesions. Rogers and Person[158] reported 19 percent of males and 18 percent of females with genital involvement.

In males the lesions are generally vesicular and usually involve the glans penis and prepuce.[76,116,132] These lesions may show bleeding and scar formation which develops between the glans penis and the prepuce and may cause phimosis.[116] Hardy and his co-workers[76] reported one patient in whom scarring lesions developed on the scrotum, and another in whom urethral stenosis occurred which required frequent dilatation.

In females, the lesions are most commonly seen on the labia major and minora, although they may rarely affect the vaginal mucosa.[76,132] Involvement of the vulva and vagina may lead to marked atrophy of the mucous membranes.[116] Adhesions may form between the labia causing considerable narrowing of the vaginal opening and in extreme cases may require surgical

intervention.[76,96,99,132,167] Very occasionally the lesions of cicatricial pemphigoid may remain localized on the mucous membrane of the vulva only, but this finding has been reported only twice.[99,167]

It is not surprising to expect and to find that genital involvement in both men,but more particularly in women, will cause impairment of sexual function.[76]

(v)(e) Rectum and Anus

The anus and perianal tissues have been reportedly involved in the four largest series of cases as occurring 11 percent,[76] 7 percent,[187] 3 percent, and 1.5 percent[158] of the time.

The most frequently reported symptom is pain and spasm,[76,116,132] although Lever[116] states that this is not usually severe enough to interfere with defecation. Occasionally bleeding will occur.[132]

Proctoscopic examination will on occasions show ulcerated lesions and it is these erosions which probably account for the spasms.[76]

(v)(f) Unusual Sites

Thomson, Lang and Craig[210] described an elderly male patient with moderately severe cicatricial pemphigoid who became deaf following the appearance of postero-superior retraction pockets in both eardums. These authors postulated that the disease process of cicatricial pemphigoid was responsible for the development of these pockets and the subsequent decline in the

patient's hearing because the development of these lesions corresponded with a severe period of his cicatricial pemphigoid. This is the only reported case of cicatricial pemphigoid affecting the mucous membrane of the middle ear.

Marks and Shuster[129] carried out an interesting study in which they biopsied the jejunal mucosa in ten patients with cicatricial pemphigoid. The important fact which emerged from their study was that the coeliac syndrome which is seen in two-thirds of patients with dermatitis herpetiformis was not seen in pemphigoid. This information may therefore be of benefit in the differential diagnosis of the two conditions in patients in whom the clinical and histological diagnosis is uncertain.

2. The Histopathology of Cicatricial Pemphigoid

As has been stated, the thorough taking of a history from, and careful clinical examination of, a patient with lesions suggestive of cicatricial pemphigoid are essential steps required before a provisional diagnosis may be made. In the vast majority of cases, however, it is the removal of lesional tissue by biopsy and its subsequent microscopic examination which yields perhaps the most important diagnostic information. Examination of pathological tissue by light, and in some cases electron microscopy is usually sufficient to enable a definitive diagnosis of cicatricial pemphigoid to be made.

(i) Lesions Suitable for Biopsy

The patient who submits to a biopsy has a right to the utmost benefit that can be derived from that procedure.[97] A number of factors need to be considered if this is to be the case, not least of which is that the fragment of tissue excised must be representative. This implies that not all lesions displayed on the integument may be suitable for biopsy if a correct diagnosis is going to be made following its microscopical examination. This is particularly true of the lesions of cicatricial pemphigoid.

As the disease runs a chronic course, and because mucosal lesions run their clinical course fairly slowly, and also because various areas of several different regions of the body may be involved simultaneously, then it is quite possible, and indeed usual, that lesions in various stages of development and degeneration will be seen. Only lesions of cicatricial pemphigoid during certain stages of their development are suitable for biopsy.

Bernstein[21] has made several suggestions regarding the general selection of soft tissue lesions for biopsy. He believes that it is apposite to avoid biopsies of obvious superficial ulcers or necrotic tissue as these are non-specific histologically and can rarely be diagnosed. As a general rule he also suggests that it is preferable to include the peripheral regions of lesions in the biopsy. Presumably because the edge of a lesion is the more likely area to show the "freshest" pathological changes associated with the disease process.

In the case of a vesiculo-bullous disease such as cicatricial pemphigoid, biopsy should preferably be performed on a fresh, intact blister.[21,138] In line with Bernstein's suggestion, it is prudent to include the periphery of a fresh bulla as well as a small zone of adjacent "normal tissue" in the biopsy.[93](Fig.IV.21) Biopsy of old, ulcerated lesions provides a low probability of providing a diagnosis because once a bulla breaks it ulcerates and the features of chronic infection and tissue necrosis mask the underlying pathological process.[138] This is particularly important when examining tissue by immunofluorescent methods to detect antibody binding sites. In older lesions the basement-membrane zone may be completely destroyed, resulting in a negative immunofluorescent reaction.[93] If an intact vesicle cannot be located, a margin of "normal tissue", together with the overhanging blister roof may suffice.[21]

(ii) Light Microscopic Appearances of Cicatricial Pemphigoid

(a) Oral Lesions

The histopathology of oral lesions of cicatricial pemphigoid is remarkably consistent but not pathognomic.[132] This is true also for representative lesions from other sites. The pattern of chronic inflammatory cell infiltrate in the connective tissue immediately beneath the basement membrane and a non-specific subepithelial vesiculation is characteristic.[124,125,132,187] The last feature is the pathological hallmark of the mucous membrane and dermal lesions of cicatricial pemphigoid.[14,138] Where a vesicle has ruptured, these pathological changes can still

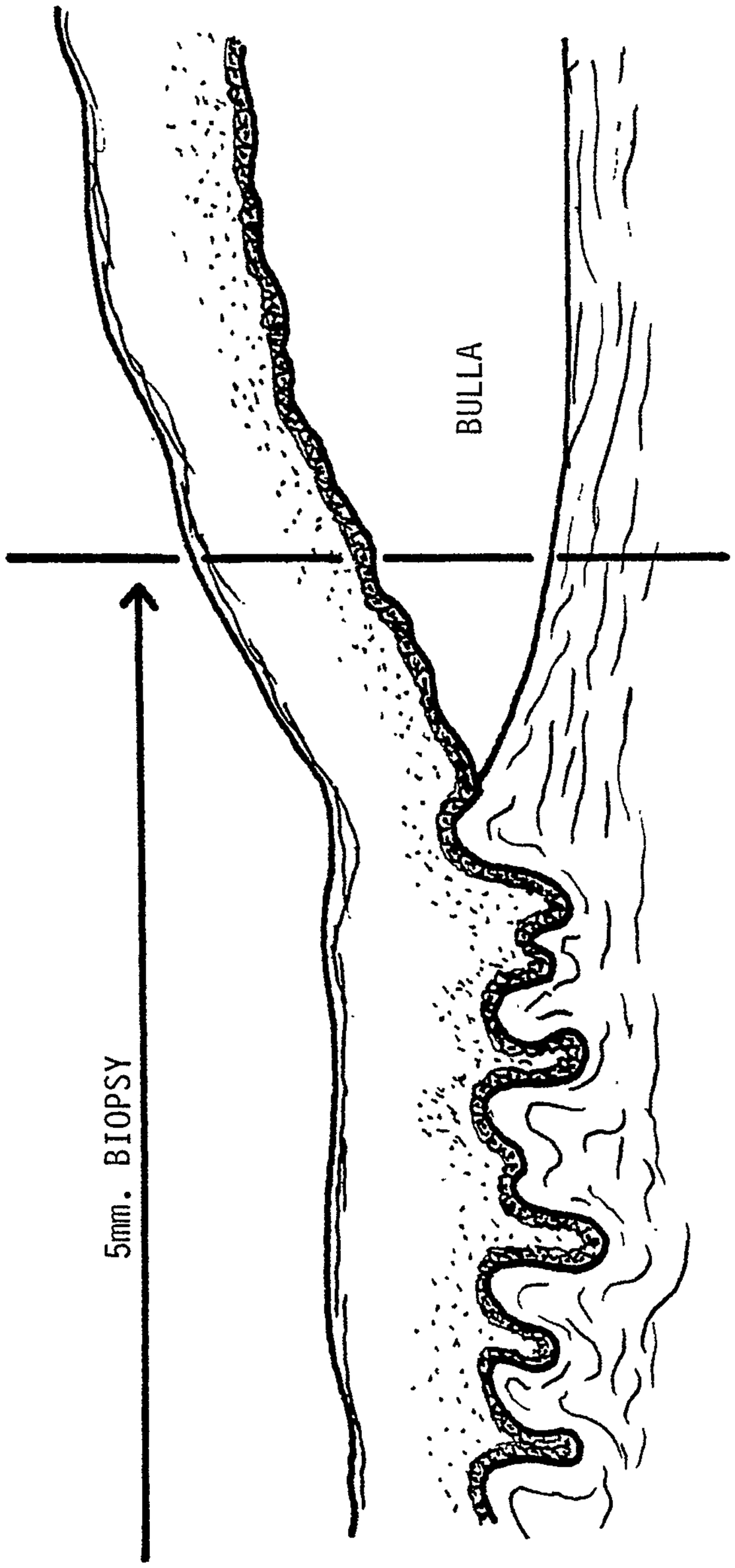

Fig.IV.21. The site indicated for the biopsy of a bulla seen in cicatricial pemphigoid. Most of the biopsy specimen (about two-thirds) should consist of mucosa adjacent to the lesion, because characteristic deposits of immunoglobulin and complement are usually most clearly seen here.

be noticed at the vesicle edge. In adjacent, clinically normal appearing tissue, the inflammatory infiltrate and the early separation of the eipthelium from the connective tissue at the basement membrane may be observed.[132]

When an intact bulla is examined with the light microscope, a definite clear-cut subepithelial vesiculation is seen, with the entire layer of stratified squamous epithelium lifted off the underlying connective tissue.[125,186](Fig.IV.22,23) The epithelium remains intact until the late stages of the life of the bulla when some atrophic alterations are visible - in some instances the epithelium tends to be thin and the nuclei of the basal cell layer become hyperchromic and pyknotic.[124,187]

With periodic acid-Schiff staining, the light microscopic basement membrane structure appears to separate with the epithelium.[125,132,187](Fig.IV.24)

The vesicle itself contains a clear material which stains slightly eosinophilic, suggestive of mucoid material.[125,186](Fig.IV.25) Any cellular element within the vesicle consists of some erythrocytes, scattered polymorphonuclear leukocytes and an occasional eosinophil.[125]

The connective tissue infiltrate in cicatricial pemphigoid is generally more massive, more diffuse, and less perivascular than in the cutaneous lesions of bullous pemphigoid.[158] The upper level of the connective tissue is usually infiltrated with a large number of neutrophils, polymorphonuclear leukocytes, lymphocytes, histiocytes, and plasma cells (typical of inflamed

Fig.IV.22. Subepithelial vesiculation with an overlying intact epithelium. Haematoxylin and eosin. (Patient 1 Table V)

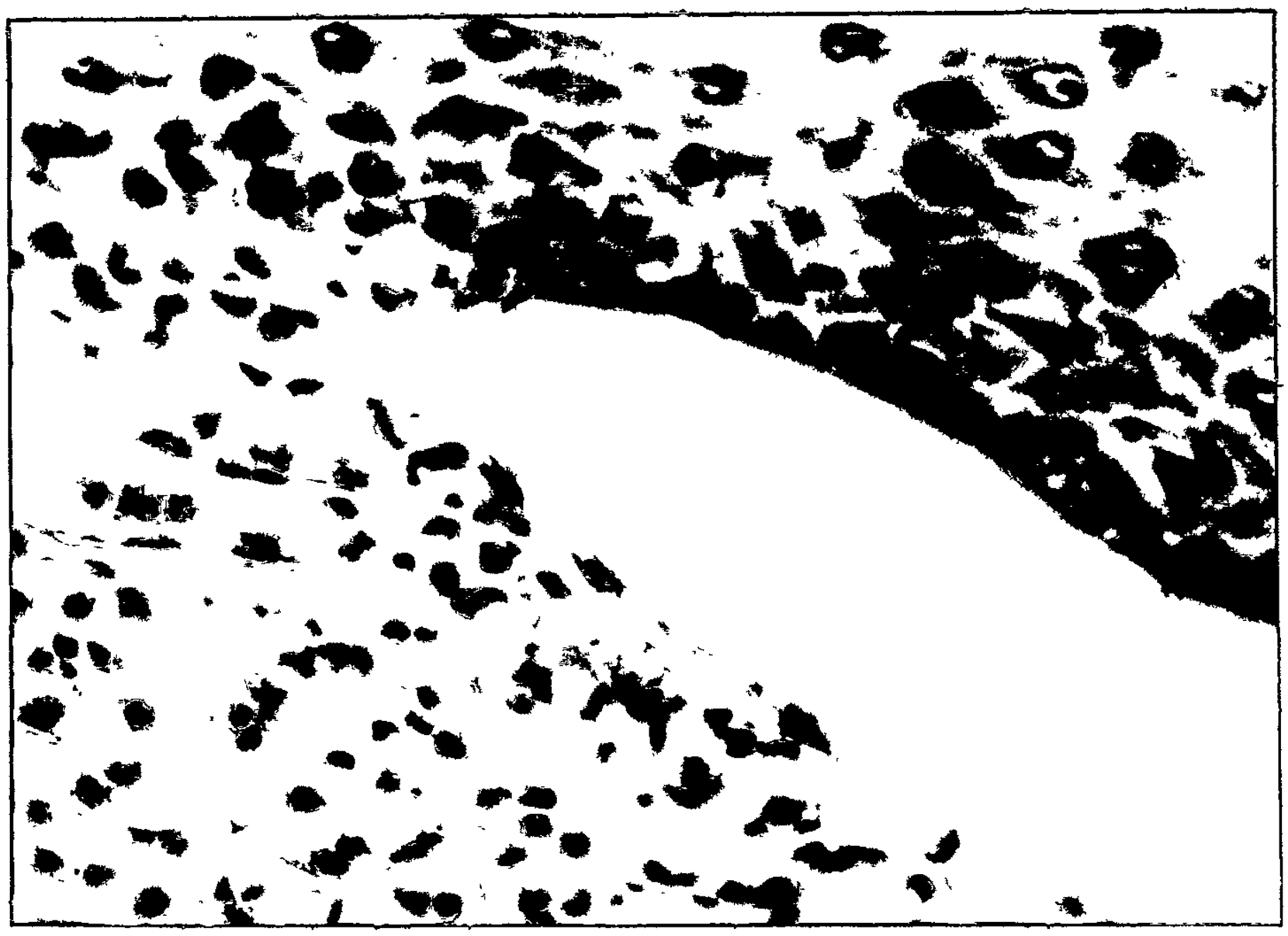

Fig.IV.23. High power of Fig.IV.22. The definite cleavage between epithelium and connective tissue is clearly seen.

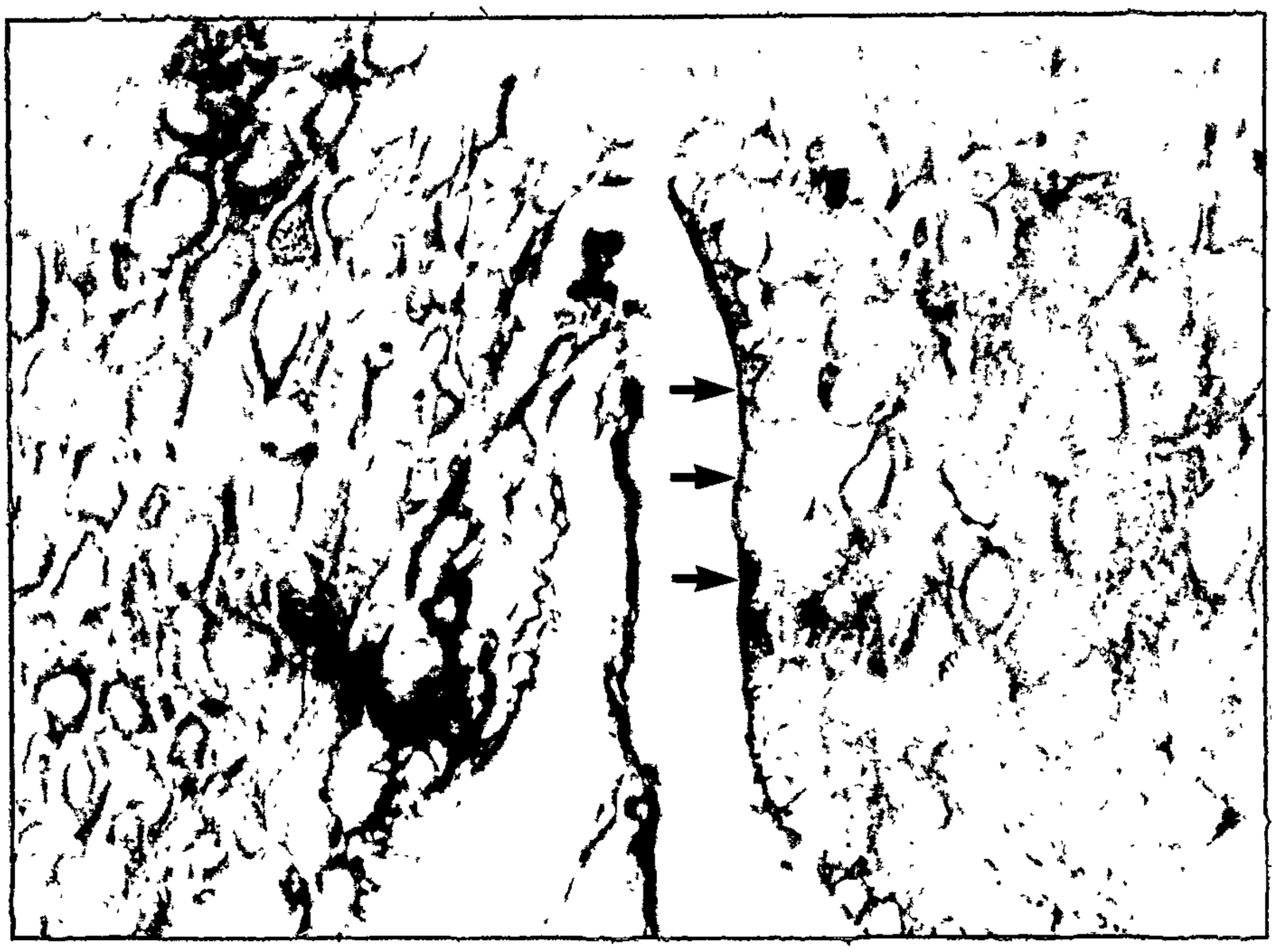

Fig.IV.24. The light microscopic basement membrane (arrowed) is attached to the epithelium. Periodic acid Schiff. (Patient 12. Table V)

Fig.IV.25. Some of the vesicle's contents have stained slightly eosinophilic. Haematoxylin and eosin. (Patient 1. Table V)

mucosal surfaces in general).[14,125,186,187](Fig.IV.26) Some eosinophils may be seen in the connective tissue but are generally much less common than in the dermal lesions of bullous pemphigoid.[158](Fig.IV.27) The deeper connective tissue tends to be relatively free of inflammatory infiltration.[187]

Disruption of the prickle cell layer (acantholysis) is not seen and differentiates cicatricial pemphigoid from pemphigus.[132,186,187] The degeneration in the upper layers of the epithelium that is seen in erythema multiforme is not present in cicatricial pemphigoid.[132] The liquefaction degeneration of the basal cell layer that causes it to be pitted and indistinct is also not observed in cicatricial pemphigoid.[183]

Biopsies taken from desquamating areas reveal stratified squamous epithelium undergoing degeneration.[125,186] The underlying connective tissue is densely infiltrated with lymphocytes, plasma cells, polymorphonuclear leukocytes and histiocytes. The polymorphonuclear leukocytes are rather dense close to the surface.[125] In some areas a definite split may be seen between the eipthelium and connective tissue.[186]

The Histopathology of Desquamative Gingivitis

The light microscopic appearance of lesions of desquamative gingivitis is essentially that of a non-specific field of epithelial degeneration and chronic inflammation.[170]

Biopsies of gingival lesions are not of diagnostic significance.[42] The typical microscopic findings are a somewhat thin, degenerating epithelium with an apparent lack of cohesion of

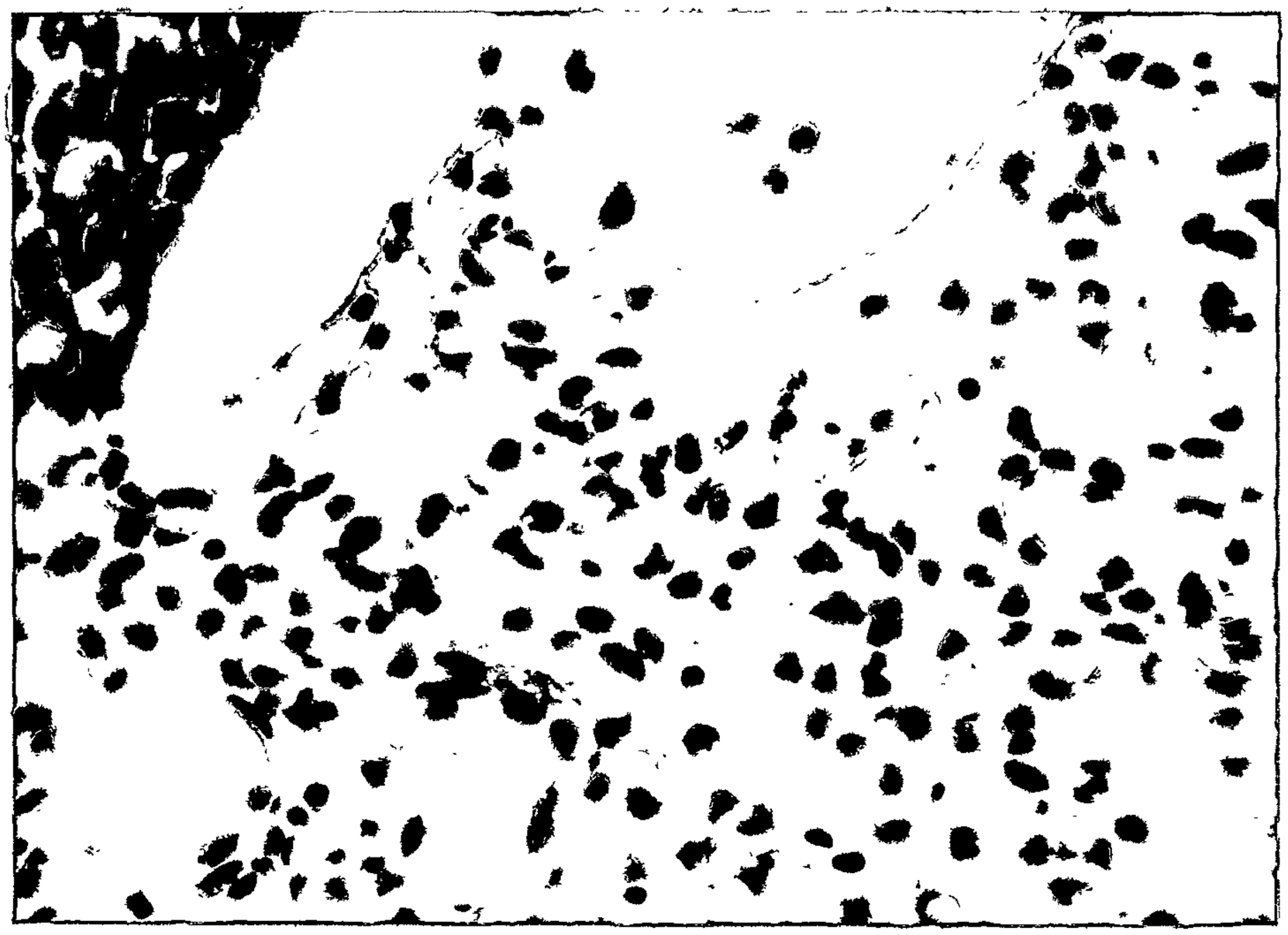

Fig.IV.26. A typical inflammatory cell infiltrate in the connective tissue beneath a vesicle cavity. Haematoxylin and eosin. (Patient 12. Table V)

Fig.IV.27. Several eosinophils are seen (arrowed) in this mucosal section. Haematoxylin and eosin. (Patient 1 Table V)

the cells of the basal and prickle cell layers. Subepithelial vesicle formation has been demonstrated in a number of reports.[123,125,170,186]

The underlying connective tissue is densely infiltrated with lymphocytes, plasma cells, and histiocytes. Scattered polymorphonuclear leukocytes are also present. This inflammatory infiltrate is diffusely spread through the upper layers of the connective tissue.

In 1969, Hall[75] reported an interesting and repetitive distribution of mast cells in biopsy specimens taken from lesions of desquamative gingivitis. He found that as well as being quite numerous, the mast cells appeared to be lined up along the basement membrane and also within the basal epithelium. Several interpretations as to their presence may be proferred. Mast cells are known to release histamine and this substance may therefore create the oedematous change responsible for bulla formation. Mast cells also contain hyaluronic acid and they may therefore be an immediate source of reparative substances.

An additional observation by Hall[75] was that when the lesions of desquamative gingivitis were treated with a topical corticosteroid ointment for extended periods, the characteristic mast cell picture was altered to a more normal distribution.

Wintroub and his co-workers,[221] despite not demonstrating the orientation of mast cells seen by Hall,[75] did, however, show progressive degranulation and involvement of mast cells as an early and continuing event in the development of the cutaneous lesions of bullous pemphigoid.

Hall[75] has to date been the only author to report such a disciplined orientation of mast cells in gingival lesions of cicatricial pemphigoid. Although not observing the ordered appearance, the author has seen occasional groups of mast cells in the connective tissue beneath gingival epithelium from biopsy specimens of several personally observed cases of cicatricial pemphigoid.

(ii)(b) Ocular Lesions

In normal eyes the conjunctiva is covered by a non-keratinized, stratified epithelium. Where it covers the tarsus and the fornix this epithelium is of the columnar type, whereas the eyeball and a narrow zone along the lid margin are covered by squamous epithelium.[149]

Norn and Kristensen[149] have examined the conjunctival epithelium by means of samples drawn from the conjunctival fluid. They found that in cicatricial pemphigoid affected eyes, the cell contents of the conjunctival fluid was characterized by an increased number of squamous and parakeratinized squamous cells. Normal columnar epithelium was being converted into squamous epithelium quite diffusely in the inferior fornix. Parakeratinization was also diffusely present and not limited to a symblepharon band or patches of leukoplakia.

Although the taking of a conjunctival biopsy has disadvantages such as causing pain, tissue damage and additional cicatricial shrinkage, Andersen and his co-workers[6] have elucidated the light microscopic features of the conjunctival mucosa affected by

cicatricial pemphigoid.

In cicatricial pemphigoid the normal columnar epithelium of the fornix and the tarsus becomes converted into squamous epithelium which shows parakeratinization or even keratinization. This conversion is diffuse and not limited to symblepharon bands. This epithelium is also often atrophic, consisting of only a few cell layers. The number of mucus producing goblet cells in the epithelium is remarkably low. Marked fibrosis is seen in the connective tissue and the basement membrane structure becomes quite variable in thickness. The cellular infiltrate consists of relatively few neutrophils, and even less numbers of eosinophils, whilst there is a moderate infiltration of lymphocytes and plasma cells.

The conjunctival epithelium, in general terms, becomes converted more or less into a dermatoid layer covering a connective tissue cicatrix.

(ii)(c) Dermal Lesions

Cutaneous biopsy specimens from patients with cicatricial pemphigoid are indistinguishable from those of bullous pemphigoid but in general show less eosinophilia.[158]

The upper dermis in bullous pemphigoid shows marked eosinophilia and a perivascular lymphohistiocytic infiltrate of variable severity. Neutrophils are also seen but in far less numbers than eosinophils.

Periodic acid-Schiff stains in bullous pemphigoid biopsy specimens show that the basement membrane structure remains

attached to the connective tissue in the vesicle.[183] But it is not reported whether this also occurs in the dermal lesions of cicatricial pemphoid.

Person and Rogers[158] have stated that because the histopathological findings in biopsy specimens of cicatricial pemphigoid are generally non-specific, the light microscopic findings may be of marginal diagnostic importance. Despite this, one must not fail to forget that Lever,[116] on histopathological grounds, initially separated cicatricial pemphigoid from the pemphigus group of lesions. It may be though, that in uncertain cases the results of electron microscopic examination of tissue and of immunofluorescent procedures may serve to make a diagnosis more definitive.

(iii) Electron Microscopic Appearances of Cicatricial Pemphigoid

(a) The Epithelial - Connective Tissue Interface

The area over which the oral epithelium contacts the subjacent connective tissue is an irregular interface at which the upward projections of the connective tissue papillae interdigitate with the downward projecting epithelial ridges.[197] The frequency, depth and shape of the interdigitations vary from region to region in both the skin and the oral mucosa, but in both are sufficient to provide a greater area of interface than is present between the surface of the epithelium and the exterior.[198]

As the site of the predominant pathological activity in cicatricial pemphigoid occurs at the epithelial-connective tissue junction, an understanding of the relationship between connective

tissue and epithelium is vital. The light and electron microscopic appearances of this region are therefore briefly described.

(iii)(b) Light Microscopic Basement Membrane

The classical concept of the basement membrane was that of a junction between epithelium and connective tissue appearing as a continuous, homogenous but structureless layer some one to two micrometres (1-2 μm) in thickness which is well demonstrated by the classical Periodic-acid Schiff procedure or silver stains. The basement membrane at a light microscopic level has been thought of as being made up of a condensation of connective tissue fibres at the upper margin of the stroma.(223)

(iii)(c) Electron Microscopic Basement Membrane (Fig.IV.28)

When viewed through the electron microscope, the epithelial-connective tissue interface is shown to be constructed of several components:(223)

(i) The electron microscopic basement membrane proper with its two layers - the lamina densa (basal lamina) and lamina lucida.

(ii) An adjacent boundary band of connective tissue fibres at the stromal side of the epithelial connective tissue junction.

Running parallel with the basal plasma membranes of the basal epithelial cells and separated from them by a relatively clear zone some 200-600 Å wide is a dense layer, 200-700 Å thick; these two layers are the so-called lamina lucida and lamina densa (basal lamina) respectively.(223) The lamina lucida contains

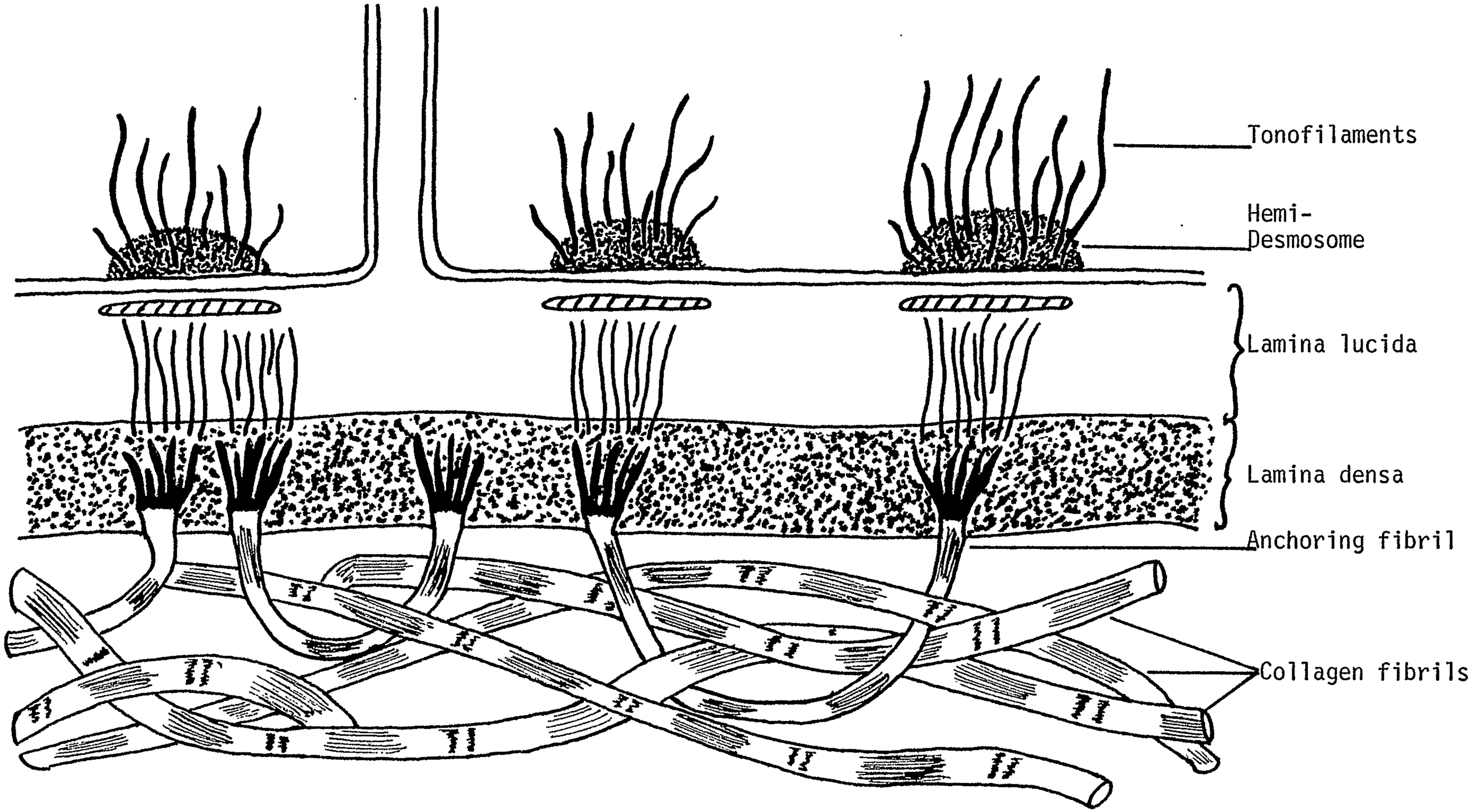

Fig.IV.28. Schematic two dimensional representation of the ultrastructure of the junction between epithelium and connective tissue.

diffuse material of low electron density and fine filaments (20-30 Å diameter) which appear to pass between the basal lamina and the plasma membrane of the basal cell. These filaments are more concentrated at the sites of hemidesmosomes.(201)

A scalloped network of densely staining fibrils is seen immediately subjacent to the lamina densa. These fibrils which have been termed anchoring fibrils measure 200-400 Å in diameter and extend for nearly 200 μm into the connective tissue.(223) They have a distinctive banding pattern but no regular periodicity.

Beneath the lamina densa the anchoring fibrils form loops(200) through which collagen fibrils pass, having taken on a course parallel to the lamina densa as they run towards the epithelium.(198) As the anchoring fibrils approach the lamina densa they break up into small groups of filaments which fan out into a spray.(202) These filaments enter the lamina densa (causing it to thicken slightly) and appear to contribute to its filamentous network. The spray of finer filaments traverses the lamina lucida and terminates opposite the intercellular plaques of the hemidesmosomes of the basal epithelial cells.(201)

From the above brief account it would appear that in ultrastructural terms the basement membrane is not a membrane at all, but rather a complex of fibrils which interlock collagen fibrils of the connective tissue, the lamina densa, lamina lucida and possibly even the epithelium. It is thus more appropriate to use the term "basal complex" when referring to the structure observed with the electron microscope.(198)

This interlocking arrangement would appear to assist in counteracting forces that tend to separate the epithelium from the lamina propria. From a purely physical viewpoint the weakest links in the basal complex are the anchoring fibrils which would therefore seem to be of significance in the pathogenesis of sub-epithelial blisters in cicatricial pemphigoid. In this respect it is of interest that in vitro experiments have shown the lamina densa to be derived from epithelium whereas anchoring fibrils are derived from connective tissue.[26]

(iii)(d) Regional Differences in the Basal Complex within the Oral Cavity

The basal complex in general appears to be better developed in non-keratinized oral mucosa. The thickness of the lamina densa is inversely related to the degree of epithelial keratinization and also decreases with age.[102,201]

Variations in size and frequency of anchoring fibrils also occurs.[201] In human gingiva they are more numerous beneath large hemidesmosomes. They also have a smaller diameter in gingiva compared to non-keratinized mucosa, where they form a more nearly continuous and regular network beneath the lamina densa. This arrangement gives the impression of a greater number of anchoring fibrils per unit length of lamina densa in non-keratinized mucosa. A similar relationship occurs in the skin.

These points are of importance in a later discussion of the areas of the oral mucosa more commonly affected by lesions of cicatricial pemphigoid.

(iii)(e) Ultrastructural Aspects of the Oral Lesions of Cicatricial Pemphigoid

Electron microscopy studies on the pathogenesis of epithelial-connective tissue separation in cicatricial pemphigoid have led to contradictory and controversial results. Perhaps an explanation for this uncertainty may be ascribed to the speed of blister formation, to the time at which biopsy is performed, to the different techniques used in specimen preparation, to the misdiagnosis of cicatricial pemphigoid as bullous pemphigoid and to the use of dermal rather than mucosal lesions. It is also indeed unfortunate that only a handful of publications has dealt with this most important aspect of cicatricial pemphigoid.

In 1971, Susi and Shklar[203] detailed the initial report in the English literature on the histochemistry and fine structure of the oral lesions of cicatricial pemphigoid. Oral biopsy specimens from twenty patients suffering from cicatricial pemphigoid formed the basis of their study. The thoroughness of their investigations is echoed by several factors. Firstly, a variety of lesions were selected and biopsied. These included early vesicles, advanced bullae, and gingival desquamative lesions. Secondly, their observations were based upon the electron-microscopic appearance of the normal tissue adjacent to the edge of the lesion; the area of beginning pathology at the edge of the lesion; and the zone of separation of epithelium and connective tissue.

Normal Oral Mucosa

At the zone adjacent to or between early vesicles the most prevalent feature is that of a normally structured epithelial-connective tissue interface. Basal cells and the upper limits of the connective tissue are apparently unaltered.

The Edge of the Lesion

One of the initial discernible differences between this area and that of normal mucosa is a slight separation of collagen fibrils of the lamina propria. Also in evidence is a marked increase in cellular activity of the lamina propria. Macrophages are seen to surround groups of collagen fibrils; lymphocytes containing well developed rough endoplasmic reticulum and Golgi saccules are present; and quite granular mast cells, seen to be extruding granules into the connective tissue, are seen occasionally in close proximity to the lamina densa.

An increase in the lamina densa, which in some areas is composed of two or more layers and extends upwards between basal cells, is also observed in this zone. Discontinuities in these multi-layers are apparent. The appearance of the basal cells is suggestive of an increased activity. The rough endoplasmic reticulum is well developed and there is an increased number of free ribosomes, mitochondria and micro-vesicles associated with the cell's plasma membrane. Projections of basal cells through the upper reaches of the connective tissue are also seen.

This observed increase in lamina densa and the apparent hyperactivity of the basal cells is possibly related and explicable.

In vitro studies by Briggman, Daldorf and Wheeler[26] showed that the formation of the lamina densa is not dependent upon the viability of the connective tissue and that it is derived from epithelial cells. This finding is also substantiated by the fact that the lamina densa is consistently initiated directly subjacent to hemidesmosomes. Therefore it would seem plausible that the increased amount of lamina densa seen at the edge of the pemphigoid lesion is due to its synthesis by the epithelial basal cells, the appearances of which - as has been stated - suggest hyperactivity. This synthesis may be a defence mechanism protecting against further and more rapid separation of epithelium from connective tissue.

Also in this zone there is a decreased prominence of anchoring fibrils. It is of interest to note that the formation of these fibrils is dependent upon the viability of the connective tissue.[26] This disappearance of anchoring fibrils at the edge of the pemphigoid lesion will obviously reduce the adherence of epithelium to connective tissue and so facilitate the development of the sub-epithelial vesiculation so characteristically seen in the fully developed bullae of cicatricial pemphigoid.

The Zone of Epithelial-Connective Tissue Separation

In this zone of actual vesiculation, large clear areas, numerous cells of the types described previously, and loosely arranged bundles of collagen fibrils appear in the upper region of the connective tissue. A clear zone (the vesicle cavity) separating the lamina propria from the epithelium is seen to contain

erythrocytes, cellular debris, and bacterial cells. Enlarged intercellular spaces separate the epithelial basal cells although they still contain a normal complement of cytoplasmic organelles. The only noticeably altered features are irregularities in cell and nuclear outline. Prominent nucleoli are also seen. Along the basal cell plasma membrane are remnants of hemidesmosomes and, in some areas, small quantities of extracellular filamentous material probably representing the remains of the lamina densa. In other areas portions of the lamina densa are observed with the connective tissue.

The issue of most importance in regard to the above observations is the fact that evidence points to the fact that the initial changes in the development of the lesion of cicatricial pemphigoid occur in the lamina densa of the basal complex, and that as the lesion develops into a frank vesicle there is disruption and splitting of the lamina densa.

In 1972, Brauner and Jimbow[24] reported the electron microscopic findings in a lesion removed from a patient with cicatricial pemphigoid. Despite the fact that their biopsy material was taken from a dermal lesion some similar observations to those of Susi and Shklar[203] were made. The basal epidermal cells showed changes consistent with those described above. In describing the appearance of the lamina densa at the far edge of the bulla they reported an apparent "smudging" and in other areas a loss of lamina densa. This would appear comparable to the duplication and discontinuity of the basal lamina at the edge of the lesion observed by Susi and Shklar.[203]

Brauner and Jimbow,[24] in describing the bulla itself, attest that the dermoepidermal separation occurred in the intermembranous space between the plasma membrane of the basal keratinocytes and the intact lamina densa. This is in contrast to Susi and Shklar[203] who have shown that fragmentation of the lamina densa occurs in the bullae of cicatricial pemphigoid. Brauner and Jimbow[24] also state that the appearances described by Susi and Shkkar[203] are entirely identical to those of bullous pemphigoid. However, according to other workers[35,70,103,171] the electron microscopic appearance of the bullous pemphigoid lesion is that of a clean separation between the plasma cell membrane of the basal keratinocytes and the basal lamina which remains intact on the floor of the blister.

The most likely cause for the contrasting findings between these two groups of authors may lie in the different type of tissue selected by each for biopsy. Susi and Shklar[203] biopsied oral mucosa whereas Brauner and Jimbow[24] sampled skin.

Caputo, Bellone, and Crosti[35] studied the ultra-structural changes in lesions of cicatricial pemphigoid taken from four patients. Both dermal and oral mucosal tissue was sampled. In all cases except one, ultra-structural appearances of both cutaneous and mucosal lesions were identical. The fourth case had only dermal lesions and the electron-microscopic appearances were identical to those seen in bullous pemphigoid. As this patient had only dermal lesions it would be erroneous to make a clinical diagnosis of cicatricial pemphigoid. It would seem more logical to presume on both clinical and

ultrastructural grounds that this patient was indeed suffering from bullous pemphigoid.

The ultrastructural appearances of the lesions of the other three patients are similar to those reported by Susi and Shklar[203] except for one difference. In the blister itself there is a complete absence of the lamina densa. This absence of lamina densa may be due to the age of the vesicle biopsied. The assumption could be made that with increasing age of the vesicle there is a continuing disintegration of the lamina densa as the epithelial cells overlying the vesicle become less and less viable. It may also be possible that because the lamina densa is disrupted and the area of tissue seen by the electron microscope is so small, that what little amount of lamina densa that has remained attached to either the basal cells or the connective tissue has been out of the field of view. Despite this apparent diversion from the lucid observations of Susi and Shklar,[203] Caputo, Bellone and Crosti[35] agree that in cicatricial pemphigoid it is the basal lamina which appears to be directly involved in the pathogenesis of the vesicle.

(iii)(f) <u>Electronmicroscopic Changes in the Conjunctival and Corneal Epithelium</u>

Despite the serious nature of ocular lesions developing in patients with cicatricial pemphigoid only one study has been made of the ultrastructural changes that occur in the conjunctival and corneal epithelium.[36]

As has been previously recorded, the clinically apparent ocular changes consist of progressive shrinkage of the conjunctiva, shortening of the fornices, and a decrease in tear volume. The subsequent course is characterised by increasing xerosis of the conjunctiva and vascularization and epithelialization of the cornea.

Normal Bulbar Conjunctiva

The conjunctival epithelium consists predominantly of polyhedral prickle cells, a few clear cells at the basal zone, and a few mucus forming goblet cells. The cells are loosely packed to form a five to six cell layer. The epithelial cells also have extremely well developed membrane infoldings in all cell surfaces and are joined by desmosomes but are not totally interdigitated. Hence the loosely connected epithelial cells have large intercellular spaces. The infolded cell membrane at the basal zone is also loosely attached to the subepithelial tissues. The lamina densa is thin and hemidesmosomes are infrequent.

Normal Corneal Epithelium

The normal corneal epithelial cells are tightly interdigitated and have no intercellular space. The epithelium lacks basal infolding and forms straight basal lines which adhere to the basal lamina with conspicuous hemidesmosomes.

A diagrammatic representation of the conjunctival and corneal epithelium is shown in Figure IV.29.

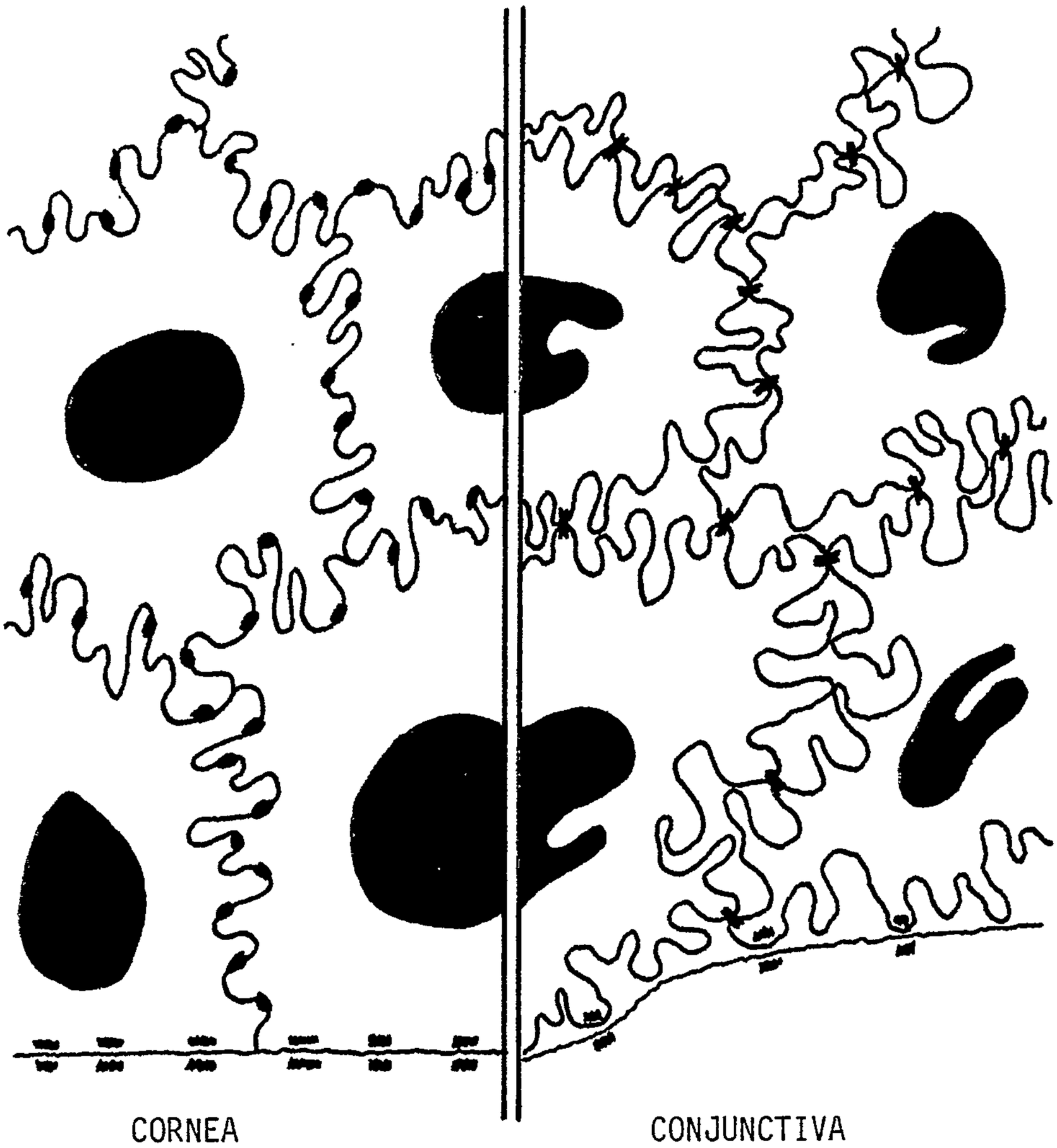

Fig.IV.29. Schematic representation of the corneal and conjunctival epithelium. The cornea has a flat base line with many desmosomes and hemi-desmosomes. The cell membranes are interdigitated. The conjunctival epithelial cells are loosely attached and infolded cell membranes do not interdigitate. The basal line is not straight and the nuclei are lobulated.

Pathological Tissue

Bulbar Conjunctival Epithelium

When viewed through the electron microscope it is apparent that all the epithelial cells, except the basal cells, have lost the loose connections and intercellular spaces. They are now held together with tight interdigitations of the cell membrane similar to that which is normally seen in the corneal epithelium. The number and size of the desmosomes are also markedly increased. Keratofibrils are also remarkably abundant but despite this there is no real keratinization occurring.

The basal cells, although maintaining normal structure and membrane infoldings, are attached by greatly increased numbers of desmosomes. Conspicuous hemidesmosomes are now also apparent at the basal plasma membranes.

The more superficial cells are markedly flattened and their cytoplasm contains abundant glycogen particles. Many of the cells are also vacuolated.

The connective tissue shows an increase in collagen fibrils and multi-layered, thick lamina densa. Short anchoring fibrils are also seen attached to the lamina densa.

Another striking difference from normal conjunctival epithelium is the absence of goblet cells with no sign of mucin formation.

From the above observations, two factors may contribute to the development of xerosis in these patients. Firstly, tightening the junctions between epithelial cells might prevent fluid accumulation in the normally occurring large intercellular spaces. Secondly, the disappearance of goblet cells and lack of mucin

production might also be a cause of dryness of the conjunctiva.

Corneal Epithelium

The corneal basal epithelial cells are extremely loosely bound and are separated from each other by wide intercellular spaces. Interdigitation, which is commonly seen in normal epithelium, is absent. As well, the basal cells have now lost their straight basal lines and show infolded cell membranes with a loss also of hemidesmosomes.

As with the basal cells of the conjunctival epithelium, the cytoplasm of the corneal basal cells contain increased keratofibrils and glycogen particles. Likewise, the surface epithelial cells are flat and are tightly joined by numerous desmosomes.

The electron microscopic changes observed in pathological tissue from the conjunctival and corneal epithelium does not offer any definite pathogenic explanations. The only changes which may be correlated with oral mucosal epithelial changes are the appearance of a multi-layered lamina densa and a loss of hemidesmosomes in the basal cells.

(iv) Immunoelectron Microscopic Findings in Cicatricial Pemphigoid

The ultrastructural localization of immunoglobulins and complement in lesions of cicatricial pemphigoid would appear to be the ultimate stage (at present) in determining the exact location of antigenic material within the basement membrane zone.

This would also allow a more precise comparison to be made with the lesions of bullous pemphigoid.

In 1975, Holubar and his associates[86] detailed the first report on the ultrastructural localization of IgG in bullous pemphigoid skin using the peroxidase-antiperoxidase multistep method. In erythematous, non-bullous skin they found that the site of IgG was both in the lamina lucida between the basal lamina and the cytomembranes of keratinocytes and also in the basal lamina proper. However, the amount of reaction product in the lamina lucida exceeded by far that seen within the basal lamina. In certain areas it also appeared preferentially associated with hemidesmosomes. In areas of skin where the epidermis had actually separated from the connective tissue (i.e. a bulla), all the reaction product was found attached to the undersurface of the epidermis. These findings would appear to correlate well with the electronmicroscopic appearances in dermal lesions of bullous pemphigoid, in which the actual area of epidermal-connective tissue separation would appear to be initiated within the lamina lucida. The findings of Holubar and his associates were corroborated in 1980 by Trost and his co-workers,[212] who again found that immunoglobulins in bullous pemphigoid lesions were preferentially distributed in the lamina lucida.

The first, and so far unique study concerning the immuno-electron microscopic findings in cicatricial pemphigoid was performed by Nieboer and his colleagues[145] in 1982. They described an elderly female patient with a vulval and peri-anal eruption associated with recurrent oral blistering. Biopsies

taken from diseased skin and oral mucosa, and the results of direct immunofluorescence indicated a diagnosis of cicatricial pemphigoid. Unfortunately the tissues selected for immunoelectron microscopic examination consisted of non-blistered rather than blistered skin and mucosa. In both tissue specimens they stated that the reaction product appeared to be above the basal lamina, in identical fashion to that found in bullous pemphigoid, but in the excellent photograph accompanying their report the reaction product is seen to be resting on the basal lamina with a quite discernible clear zone (presumably the lamina lucida) visible between the basal lamina and the basal cell cytoplasmic membrane. Apart from the possible misinterpretation evident in this report, a basic flaw in the selection of tissue for detection of immunoglobulin is apparent. Nieboer and his co-workers[145] selected, in part, non-blistered skin for their study. It is clear that non-blistered skin from patients with cicatricial pemphigoid does not show immunoglobulin or complement deposition along the basement membrane zone.[107] In contrast normal skin of patients with bullous pemphigoid is positive for in vivo bound immunoglobulin and complement.[107]

Several possible explanations therefore arise to discern the apparent contradictions expressed in this study.[145] Firstly, the patient described may have been misdiagnosed and was indeed suffering from bullous pemphigoid. This, however, appears unlikely; from the clinical description of the lesional involvement the patient almost certainly was suffering from cicatricial pemphigoid. Secondly, as has been alluded to, there is the

uncertain interpretation of the site of the reaction product within the basement membrane zone (as shown in the article's photograph). Unfortunately, no reference is made as to whether the photograph is of skin or oral mucosa. Notwithstanding the location of the tissue depicted, the site of the reaction product appears to be in the basal lamina and not above it as described in the text. This appearance would seem to correlate well with the electron microscopic appearances of the lesions of cicatricial pemphigoid previously described.

It is clear that uncertainty exists as to the ultrastructural localization of immunoglobulins and complement within the lesions of cicatricial pemphigoid. It is difficult to assume any degree of certainty on the basis of one rather doubtful study.[145] To determine these ultrastructural sites of immunoglobulin and complement deposition it will be necessary to examine a number of lesions of cicatricial pemphigoid. It will also be necessary to examine various areas of tissue from patients with cicatricial pemphigoid - in particular pre-lesional, peri-vesicular and also frankly vesicular mucous membrane. This is an obvious area for future study which will undoubtedly assist in the more complete understanding of cicatricial pemphigoid and also in its differentation from bullous pemphigoid.

3. The Immunopathology of Cicatricial Pemphigoid

(i) The Concept of Autoimmunity

Immunology is one of the newest fields in the bio-medical sciences. In this century, it has progressed from a relative

handful of workers performing the first experiments on immunity to become a major area of study in preventing, treating and diagnosing disease. Its applications are multitudinal and its possibilities seem innumerable.

Early immunologists at the turn of the century, following the teachings of Paul Ehrlich, could not conceive that the body could react against components of its own tissues with an immune response. At that time, it was considered that all immunological reactions were potentially damaging and that the production of an autoimmune state would naturally result in the destruction of the target tissue. This concept was described by Ehrlich as "horror autoxicus".(213) It is now known that under certain circumstances, the body can overcome this horror autoxicus and develop autoantibodies or an autoimmune cellular reaction against its own tissues.

Persons may sometimes produce antibodies to their own antigens. When autoimmune antibodies are secreted by plasma cells, the result may be an autoimmune disease.(61)

To document that autoimmunity causes tissue damage, it is essential to fulfil two criteria.(134) Firstly, a host immune response must occur towards autologous tissue antigen. Secondly, this immune response must be responsible for causing tissue damage. Two general types of autoimmune disease are known to exist.(134) Firstly, autoantibody may react against soluble host protein forming immune complexes which subsequently induce vasculitis. Examples of this type of autoimmune disease are systemic lupus erythematosus and rheumatoid disease. Secondly,

autoantibodies or sensitized T-lymphocytes may react against fixed tissue antigens with subsequent destruction of that organ. Examples of this type of autoimmune disease include thyroiditis and Sjögren's Syndrome.

In similar terms to the above, autoimmune disease may be described as being organ-specific or non-organ-specific.[172,181] In organ-specific disease, usually a single organ is involved and a single type or a small number of autoantibodies are found. Thyroiditis is an organ-specific autoimmune disease. In non-organ-specific disease a wide spectrum of lesions and autoantibodies is found, as for example in systemic lupus erythematosus. Some disorders occupy an intermediate position in which lesions tend to be localized to a single organ but the autoantibodies are non-organ-specific. This classification has lead to the development of a concept of an autoimmune disease spectrum. (See Table IV.1.)

(i)(a) Possible Causes for Development of Autoimmunity

Several theories have been postulated to explain the possible causes of the development of an immune reaction against "self" antigens. The exact mechanism or mechanisms, however, remain unclear. In brief, these various hypotheses are as follows:[61]

* A self-antigen from an immunologically privileged site (brain, eye lens, or testes) may have an altered distribution in which lymphocytes may encounter it for the first time.

* Biochemical alteration of a self-antigen may present a new foreign molecule to the immune system.

TABLE IV.1. SPECTRUM OF AUTOIMMUNE DISEASE

ORGAN SPECIFIC				NON-ORGAN SPECIFIC
Hashimoto's Thyroiditis	Juvenile diabetes	Autoimmune haemolytic anaemia	Ulcerative colitis	Systemic lupus erythematosus (SLE)
Thyrotoxicosis	Pemphigus vulgaris		Sjögren's syndrome	Discoid LE
Pernicious anaemia	Pemphigoid			Scleroderma
Addison's disease				Rheumatoid arthritis

* Introduction of a foreign molecule that is similar to a self-antigen could lead to an immunological cross-reaction.

* Abnormal "forbidden" lymphocyte clones can emerge that are primed to produce anti-self antibodies. Suppressor T-lymphocytes may malfunction and allow proliferation of "forbidden" B-lymphocyte clones.

* Incorporated antigens (that is, viral antigens on the surfaces of cell membranes) may alter tissue in some way and cause immune responses that are indistinguishable from autoimmune reactions.

(ii) Immunological Techniques in the Diagnosis of Cicatricial Pemphigoid

The vast majority of immunological tests are based on the detection of specific defence mechanisms.[84]

The specific immune mechanisms of the body are based either on humoral antibody activity or cellular activity. Both of these immune activities are lymphocyte derived; humoral antibodies being produced by B-lymphocytes and cellular defence mechanisms being conducted by T-lymphocytes. Immunological procedures designed to diagnose certain diseases are based on these two interdependent systems.

The immunological techniques employed in the diagnosis of cicatricial pemphigoid, and other vesiculo-bullous disorders, are based upon the identification of antigen-antibody reaction sites. Specifically, these tests are known as immunofluorescent techniques.

The basic principle of the fluorescent antibody technique is simple.[90] Antigenic material present in the tissue (for example, in the cell, at the cell margin, or at the basement membrane zone) will react specifically with its related antibody. This immunological reaction results in the deposition of minute amounts of specific antibody over those areas of a tissue section where the antigen is present. With the incorporation of a fluorescent dye in the reaction, the microscopic deposits of antibody are visible as a brilliant yellow-green light under the fluorescent microscope.

The test may be employed in two ways - the direct and the indirect methods. The direct test is used for the detection of in vivo bound immunoglobulins and complement in biopsy specimens, whereas the indirect test is employed to detect antibodies in a patient's serum.[148] The crucial difference between the two tests is the site of the fluorescent dye label. In the direct test the label is on the antibody, whereas in the indirect test the label is carried on the anti-antibody molecule.

(ii)(a) <u>The Direct Test</u>[84](Fig.IV.30)

This test is used for the identification and localization of immune antigen-antibody complexes or of autoantibody in tissues.

(ii)(b) <u>The Indirect Test</u> (Fig.IV.30)

This test is designed to show the presence of specific auto-antibody in serum.[84] In this test, dilutions of the patient's serum are placed on cryostat-cut frozen sections of normal

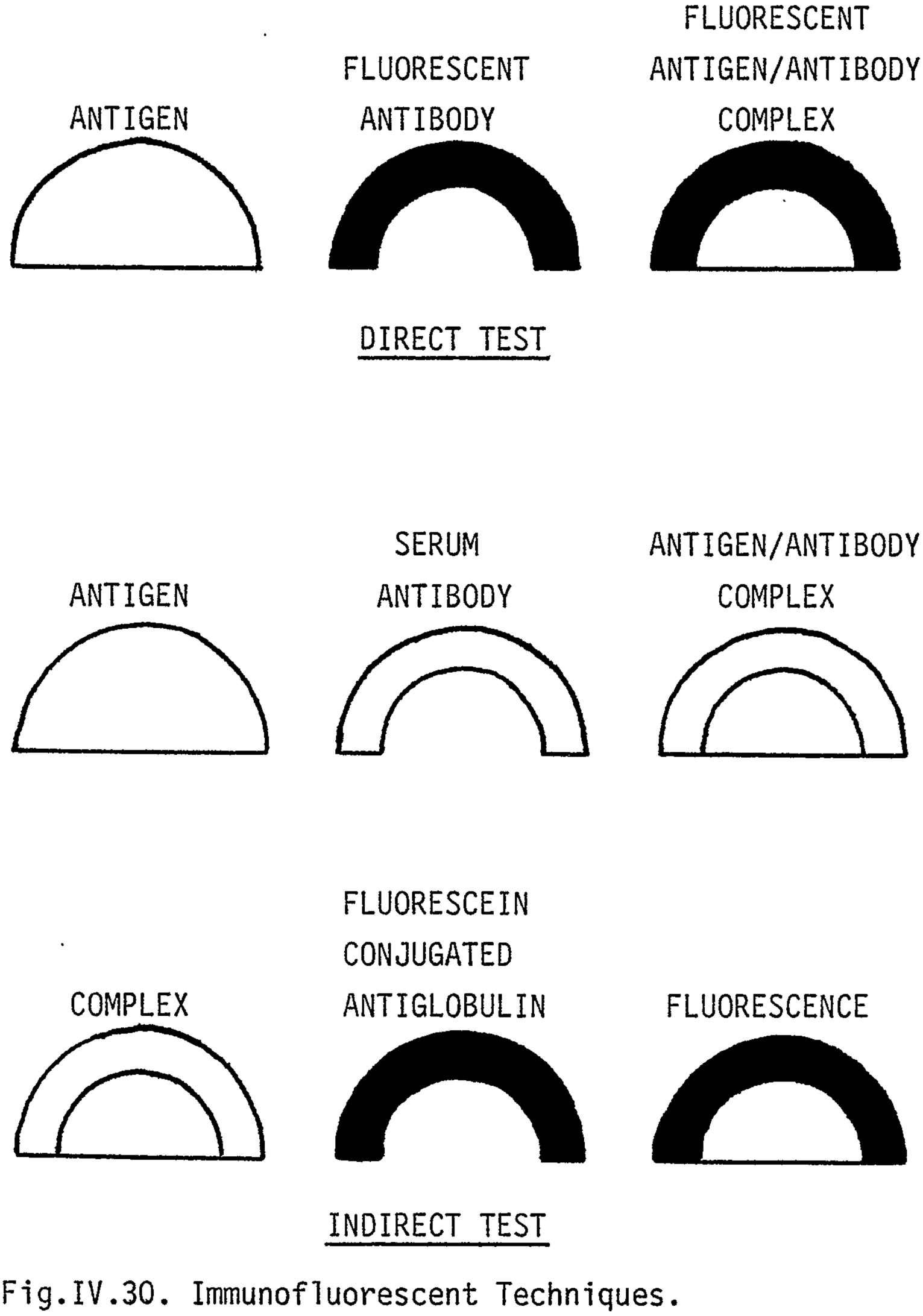

Fig.IV.30. Immunofluorescent Techniques.

mammalian tissue (usually monkey oesophagus) and allowed to incubate. During incubation, serum antibodies to specific tissue antigens attach to these tissue components. The tissue sections are then washed to remove free, unbound serum constituents. The serum antibodies can then be visualized by reaction with an anti-immunoglobulin (usually IgG) "conjugate". In the preparation of such a conjugate, fluorescein (a fluorescent dye) is chemically bound or conjugated to antibodies specific for human immunoglobulin.[148] A drop of conjugate is placed on the tissue section and allowed to incubate. These conjugated antibodies bind to their corresponding antigens, which are the antibodies from the patient's serum which have fixed to the tissues. Finally (after appropriate processing), the sections are examined with the fluorescent microscope.

(ii)(c) Specimens Indicated for Immunofluorescent Studies

The value of immunopathological tests corresponds to the judiciousness with which specimens are selected for study.[91,148]

Serum Samples

At least 8 to 10 mls. of blood, without anticoagulants, should be collected.[91,93,148] It is preferable to immediately separate the serum.[93,148] If no facilities are available for separating serum, then clotted blood may be sent to the laboratory, as long as it is not frozen because this causes haemolysis.

Biopsies

Two methods are now in use for handling biopsy material. Quick freezing is the most widely used method and is generally recommended.[91,93,148] Another method of transporting biopsy tissue is in a special holding solution. Biopsy material can either be quick frozen by placing the tissue directly into liquid nitrogen or by first placing the tissue into a container which is then placed in a slush of dry ice mixed with acetone. No matter what method is chosen the tissue must remain frozen until it reaches the laboratory for processing.[91,93]

As has been stated, the site of biopsy in the oral cavity must be carefully selected. When oral lesions of cicatricial pemphigoid are biopsied, at least a 5 mm. specimen should be taken from the edge of a lesion, preferably a fresh lesion. (Fig.IV.21) If an old lesion is biopsied the basement membrane zone may have been completely destroyed, resulting in a negative immunofluorescent finding.[91]

(iii) Immunofluorescence Tests: Findings in Cicatricial Pemphigoid

The original and subsequent immunofluorescent studies of biopsy specimens and sera taken from patients with cicatricial pemphigoid failed to reveal basement membrane zone antibodies which are present in most cases of bullous pemphigoid. The lack of these basement membrane zone antibodies cast some doubt on the suggestion that a relationship existed between the two diseases.[15]

In 1972, however, Bean and his associates[17] detailed the first group of patients with cicatricial pemphigoid in whom direct immunofluorescent tests demonstrated the presence of basement membrane zone in vivo fixed immunoglobulin and complement, morphologically indistinguishable from that seen in bullous pemphigoid. They were not able to demonstrate the presence of circulating basement membrane zone antibodies in the serum of these patients. Dantzig[54] in 1973 was the first to report a case of cicatricial pemphigoid in which circulating antibodies to the basement membrane zone were demonstrable.

(iii)(a) Direct Immunofluorescence

As has been stated, Bean and his colleagues[17] demonstrated the existence of in vivo fixed immunoglobulins along the basement membrane zone of the oral mucosa, conjunctiva, and skin in three out of four patients with cicatricial pemphigoid. These observations have been confirmed by other investigators and are summarized in Table IV.2.

The deposition and appearance (using a "fluorescent microscope") of immunoglobulins with or without complement and fibrin along the basement membrane zone in a linear and continuous pattern, indistinguishable from that found in bullous pemphigoid, is to be interpreted as being a positive result using the direct immunofluorescent test. (Fig.IV.31)

Most authors would now seem to agree that approximately 80 percent of mucosal biopsy specimens will show positive direct immunofluorescence in the basement membrane zone.[67,108,132,147,148]

TABLE IV.2 SUMMARY OF IMMUNOFLUORESCENT FINDINGS IN CICATRICIAL PEMPHIGOID

Authors	Direct I.F. Findings					Indirect I.F. Findings		
	No. of biopsy specimens examined	Positive		Negative		No. of Sera examined	Positive	Negative
		Skin	Mucosa	Skin	Mucosa			
Hardy et al(76)	2			2	-	15		15
Brody & Weupper(28)	4			4	-			-
Bean et al(17)	4	2	2	2	1	4		4
Heydenreich et al(82)	2	1	-	1		2		2
Holubar et al(85)	5	4	-	1		5		5
Dabelsteen et al(50)	6	-	4		2	8	7	1
Griffith et al(74)	11	-	7		4	12		12
Tagami & Imamura(204)	1	1	-			1	1	
Herron(81)	1	1	1			1		1
Foster & Nally(67)	7	-	6			7	2	5
Rogers et al(168)	23	-	19		4	23	2	21
Dantzig(54)	1	1	-			1	1	
Jordon et al(100)	5			-	5	5		5
Bean(13)	8	3	4	5	2	8	3	5
Laskaris et al(107)	33	1	32	32	1	33	12	21
Person & Rogers(158)	31	-	9		22	31	3	28
Marx & Sanders(132)	1	-	1		1	1		1
Nisengard et al(147)	1	-	1		1	1		1
Mitchell & Smith(138)	13	-	7		6	-		-
TOTAL	159	14(9%)	93(59%)	47	49	158	31(20%)	127

- Not performed

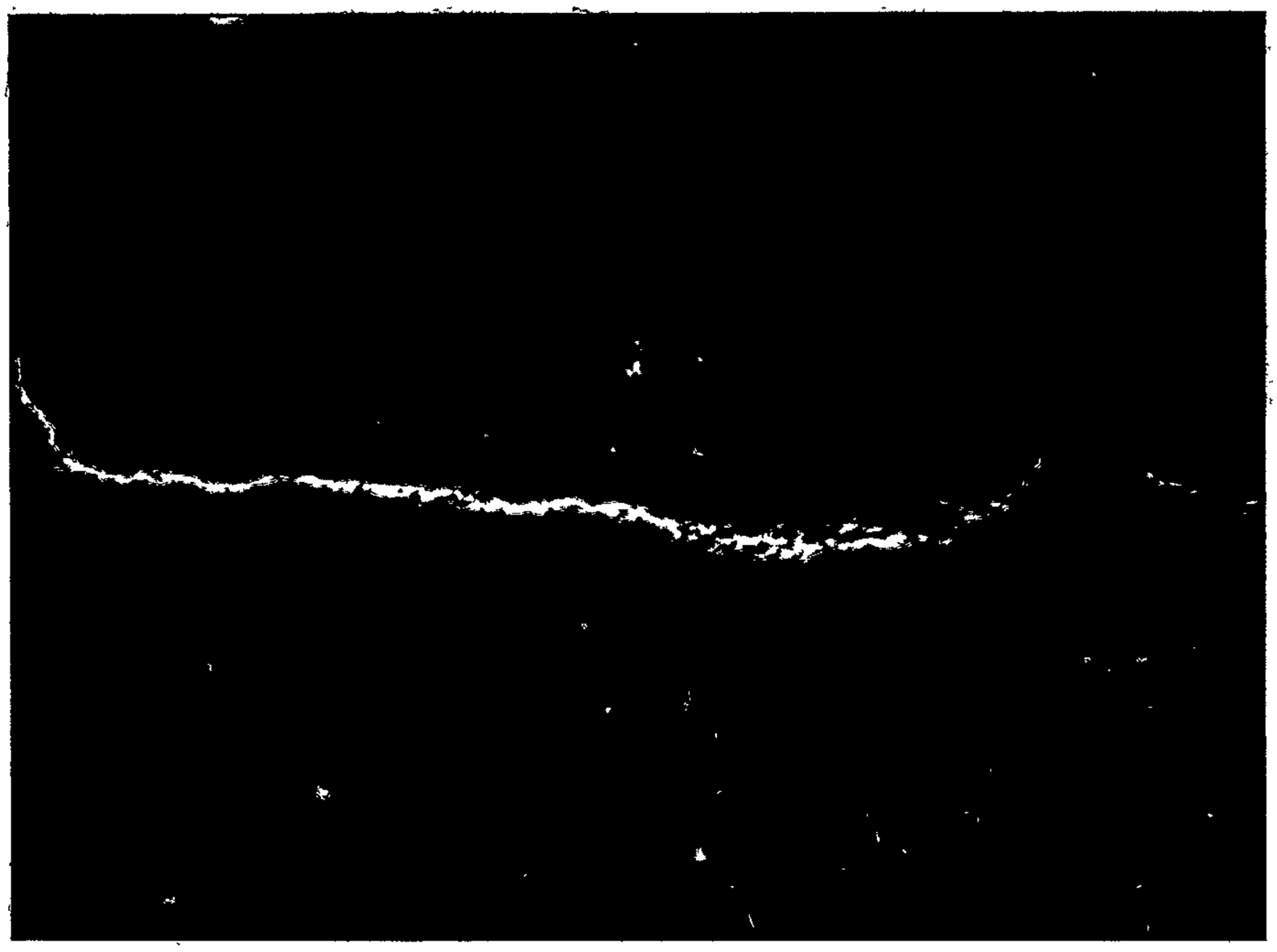

Fig.IV.31. Positive direct immunofluorescence. The bright green band is a linear deposit of complement along the basement membrane zone. The epithelium is towards the top of the illustration. (Patient 1.Table V)

Antisera specific for reaction with suspected patient immunoglobulins deposited in their biopsy tissue are available for IgG, IgA, IgM, and C3 on a routine basis in most facilities capable of performing immunofluorescent studies. Of these, the most consistent findings are the detection of anti-IgG or C3 at the basement membrane zone.[15,67,107,108,132,138,168] Less consistently IgA and IgM are demonstrated.

It would appear that it is mainly the classical pathway of complement activation at the basement membrane zone that is involved in cicatricial pemphigoid, although activation of the alternative pathway may occur.[83,158,168]

An interesting finding reported by several authors[74,158] is that when a fresh vesicle is examined, the fluorescence is observed on both the roof and the floor of the vesicular space, implying an actual splitting of the basement membrane zone. This observation would appear to correlate with the electron microscopic findings of cicatricial pemphigoid discussed previously. It is also important to note that the characteristic deposits of immunoglobulins and complement which precede the formation of vesicles can be seen most clearly at the edge of a fresh developing lesion.[91,108] This would seem to corroborate the belief that in taking a biopsy for immunofluorescent testing, it is advisable to include both the edge of a vesicle and a margin of peripheral tissue.

As far as direct immunofluorescent testing of the dermal lesions in patients with chronic localized pemphigoid (Brunsting-Perry type) is concerned, it is clear that positive results are

obtained in the majority of cases.[77,94,135,146,161,218] It is also clear that normal skin from patients with cicatricial pemphigoid does not show immunoglobulin or complement deposition along the basement membrane zone.[107] In contrast, in-vivo immunoglobulin and complement deposition occurs in the normal oral mucosa and normal skin in patients with bullous pemphigoid.[107]

Author's Experience

Oral mucosal biopsy specimens were studied using standard immunofluorescent techniques and conjugates.[108] It was found that the oral mucosal tissue excised from seven of the fourteen patients with cicatricial pemphigoid studied with the direct immunofluorescent technique demonstrated in-vivo fixed IgG, IgA, and complement (C3) along the basement membrane zone (See Table V). IgM was not demonstrated.

Four of these seven patients had involvement of sites other than the oral mucosa most notably the skin (in three of the four cases) and the eyes (in three of the four cases).

(iii)(b) Indirect Immunofluorescence

Early efforts failed to show circulating anti-basement membrane zone antibodies in patients with cicatricial pemphigoid, and this was a strong argument against the hypothesis that cicatricial pemphigoid and bullous pemphigoid are closely related.[15,17,82] Furthermore, the lack of serum antibodies in cicatricial pemphigoid raised some doubts regarding the possible pathogenic role of an autoimmune process in the disease.

Recently, however, circulating anti-basement membrane zone antibodies have been detected by several investigators in the serum of patients with cicatricial pemphigoid(Table IV.2), and this fact gives impetus to the view that the two types of pemphigoid are closely related.

In bullous pemphigoid, antibodies frequently of high titre (greater than 160) are found in more than 80 percent of cases.[93,147,158] In cicatricial pemphigoid, a lower incidence and a lower titre of serum antibodies is demonstrable - being found in approximately 30 percent of cases.[107,158,221] It is of particular interest to note that the circulating antibodies of cicatricial pemphigoid have the same staining pattern as that found in bullous pemphigoid.[13,54,107] Several authors have also observed that the detectable level of antibody titre in patients with cicatricial pemphigoid seems to correlate with the activity of the disease but not with its severity in terms of extent.[132,147,160,204] Bean[13] and Laskaris and Angelopoulos[107] have also shown that the circulating antibodies of cicatricial pemphigoid may show more specificity for the patient's own tissues, and hence their detection with heterologous squamous epithelium is less likely to be successful. Another feature of interest as regards patients with cicatricial pemphigoid who have detectable circulating anti-basement membrane zone antibodies is that most are women with extensive disease.[13,50,54,107,158,160,204]

(iv) The Significance of Immunofluorescent Findings in Cicatricial Pemphigoid

The demonstration of in-vivo bound basement membrane zone immunoglobulins and complement, morphologically indistinguishable from those of bullous pemphigoid, in skin and oral mucous membrane in patients with cicatricial pemphigoid, and circulating anti-basement membrane zone antibodies in the sera of these patients provides support for a unitarian concept.[15] Several features of bullous and cicatricial pemphigoid need, however, to be explained:

(a) The very low incidence of circulating anti-basement membrane zone antibodies in cicatricial pemphigoid when compared with bullous pemphigoid.

(b) The high incidence of mucous membrane involvement in cicatricial pemphigoid compared with bullous pemphigoid.

(c) The relationship between cicatricial pemphigoid, localized chronic pemphigoid, and bullous pemphigoid as regards a pemphigoid disease spectrum.

A number of theories have been hypothesized in order to help explain the above observations, although none have been adequately substantiated.

According to some investigators,[13,15,69,100] in cicatricial pemphigoid all anti-basement membrane zone antibodies may be bound to the homologous basement membrane zone antigen, early in the development of the disease (or after the onset of a relapse), and therefore are undetectable in the circulation as none are available for release into the serum. In most cases of cicatricial

pemphigoid, a limited process as compared to bullous pemphigoid, it may be that the extent of involvement is not sufficient to produce enough antibody to be released into the serum and hence be detected.[13,17,69,107] Other investigators have proposed that indirect immunofluorescent techniques that are at present routinely used may not be sufficiently sensitive to demonstrate very low titres of circulating antibodies.[45]

The fact that mucous membranes are commonly affected in cicatricial pemphigoid might be due to the nature of the antibodies.[15] In this regard it is important to note that Bean[13] and Laskaris[107] were able to demonstrate a number of patients in whom circulating anti-basement membrane zone antibodies were detectable only in normal human oral mucosa substrate, whilst negative results were obtained when animal and normal skin substrates were used. These findings support the concept that the circulating antibodies in cicatricial pemphigoid are in fact organ and species specific and are directed against antigenic determinants that are present mainly in the oral mucosa or other mucous membranes and very rarely in the skin.[15,69,107]

It has been suggested by Chorzelski and Beutner[40] that mucous membranes and skin not only have certain antigenic determinants in common but also that additional determinants are present in the mucosa and are absent in the epidermis of some individuals. If this hypothesis is true then the primary antigenic target in cicatricial pemphigoid lies predominantly in the oral mucosa, the conjunctiva, and other mucous membranes. The disease may involve the skin only when the antigenic

determinants are in common with those of the mucous membranes. The reverse would be true in bullous pemphigoid where the primary target organ is the skin, with mucous membrane involvement occurring only occasionally.

The pathophysiological significance of the immunoglobulins and complement demonstrated in cicatricial pemphigoid remains to be fully explained; however, with the recent demonstration of circulating antibodies, as detailed above, an autoimmune aetiology appears most likely.

Because of the similar immunofluorescent findings in cicatricial, localized chronic, and bullous pemphigoid, it has been proposed that these three diseases are related and represent a spectrum of disease.[17,94,146] Bean and his associates[17] first suggested that cicatricial pemphigoid and bullous pemphigoid represent a disease spectrum analagous to that seen in lupus erythematosus. At one end of the spectrum is cicatricial pemphigoid, which, like discoid lupus erythematosus, shows principally tissue-fixed antibodies and only occasionally circulating antibodies.[13,204] The latter are represented by anti-basement membrane zone antibodies for cicatricial pemphigoid and anti-nuclear antibody for discoid lupus erythamatosus respectively. Cicatricial pemphigoid results in scarring as does discoid lupus erythematosus. At the other end of the spectrum is bullous pemphigoid, which, analagous to systemic lupus erythematosus, often demonstrates both tissue-fixed and circulating antibodies. Bullous pemphigoid rarely results in scarring and systemic lupus erythematosus is also most often associated with non-scarring skin lesions.

In 1977, Michel and his associates[135] described the immunofluorescent findings in six patients with localized chronic pemphigoid (Brunsting-Perry type). All these patients had positive direct immunofluorescence for IgG at the basement membrane zone in a pattern morphologically indistinguishable from that which is characteristic of bullous pemphigoid and cicatricial pemphigoid. One patient also had circulating anti-basement membrane zone antibodies. On the basis of the clinical histological and immunofluorescent findings in patients with localized chronic pemphigoid, they proposed that this disease is a part of the cicatricial pemphigoid-bullous pemphigoid spectrum. This concept was supported also by the findings of Jacoby and his associates[94] and later by Niebor and his associates.[146]

From a practical and theoretical point of view, localized chronic pemphigoid, cicatricial pemphigoid and bullous pemphigoid should be considered as three distinct forms of the one pemphigoid syndrome.[146] Their most important characteristic features are summarized in Table IV.3.

Localized chronic pemphigoid differs from bullous pemphigoid in the absence of circulating antibodies directed against the basement membrane zone, the negative direct immunofluorescent findings in uninvolved skin, the scarring and the clinical course. Localized chronic pemphigoid and cicatricial pemphigoid share important features: the chronic recurrent course, the scarring, the low incidence of circulating antibodies, the usually negative direct immunofluorescent findings in uninvolved skin, and the concomitant occurrence of IgG and IgM in the basement membrane zone.

TABLE IV.3 CLINICAL, HISTOPATHOLOGICAL, AND IMMUNOFLUORESCENT FINDINGS IN THE PEMPHIGOID SYNDROME*

	Clinical Characteristics				Histopathology	Immunofluoresence		
	Involvement %		Scarring			direct %		indirect %
	skin	mucosa	skin	mucosa		Ig	C	serum antibodies
Cicatricial Pemphigoid	30	100	±	+	subepithelial bulla	60-80	60-80	20-30
Localized Chronic Pemphigoid	100	-	+	-	subepidermal bulla	+**	+**	-**
Bullous Pemphigoid	100	30	-	-	subepidermal bulla	100	100	80

* Modified from Nieboer, Roeleveld & Kalsbeek.(146)

** Too few data available to calculate a percentage

(v) Unusual Immunopathological Findings in Cicatricial Pemphigoid

(v)(a) Pemphigus-like Antibodies

In 1974 Cram and his associates[49] observed two patients with clinical and direct immunofluorescent features of cicatricial pemphigoid in whom indirect immunofluorescence revealed a circulating antibody directed to the intercellular area of epithelium, a feature characteristic of pemphigus vulgaris. The explanation offered to explain this finding was that the circulating antibodies found in these patients represented a pemphigus-like antibody similar to that found in burns, Lyell syndrome, and certain other skin diseases. It was thought that acute epithelial injury may have stimulated such antibody production in these cases.

A similar case of circulating pemphigus-like antibodies was described by Kumar and his associates.[106] Their additional finding that complement-fixing intercellular antibodies appeared afforded a valuable clue; notably, pemphigus-like antibodies can be distinguished from true pemphigus antibodies not only by their failure to bind in vivo but also by their capacity to fix complement.

(v)(b) H L A Antigens in Cicatricial Pemphigoid

Substantial evidence is accumulating that HLA antigens are correlated with certain disease entities in man and more particularly those of an autoimmune nature.[139] In this regard Mondino and his associates[139] performed histocompatibility

antigen tests on a number of patients with cicatricial pemphigoid to determine if one or more HLA antigens were more prevalent in this group. This study revealed an increased frequency of HLA-B12 and A3 in patients with cicatricial pemphigoid; however, this was statistically significant only in the case of HLA-B12. The results of this study suggest that HLA-B12 and possibly HLA-A3 are genetic markers for cicatricial pemphigoid.

Unfortunately, no further studies of this interesting phenomenon have been reported in the literature.

V PERSONALLY OBSERVED CASES

1. Material
2. Observations
3. Age and Sex
4. Duration of Symptoms before Diagnosis
5. Initial Complaint
6. Clinical Findings
7. Diagnosis

V PERSONALLY OBSERVED CASES

1. Material

Fourteen cases of cicatricial pemphigoid were diagnosed in the Department of Oral Medicine and Oral Surgery (Faculty of Dentistry, University of Sydney) between April, 1968 and July, 1980.

Biopsies of oral mucosa were performed in all cases. In twelve of these the histological appearances confirmed the clinical diagnosis, whilst in the remaining two (No. 3 and 9) the microscopic features were not specific. However, the clinical findings in these two cases were considered to be so characteristic of cicatricial pemphigoid as to justify their inclusion in this review.

2. Observations

The data are summarized in Table V.

3. Age and Sex

The ages of the patients ranged from eighteen to sixty-eight years at time of reported onset of the condition. The mean age was fifty-six years. If, however, patients No. 6 and No. 10 are excluded, then the mean age rises to sixty-one years.

Nine of the patients were female and five were male, indicating a female to male ratio of approximately 2:1.

TABLE V

Summary of findings in 14 patients aged 18-68 years with Cicatricial Pemphigoid 1968-1980

Patient No.	Sex	Age At Onset	Duration Before Diagnosis	Presenting Complaint	Intact Bulla	Subsequent Sites of Lesions	Histopathology	Immunopathology*
1	F	50	10 yrs	blisters:eyes & mouth	No	skin,eyes,larynx	sub-epithelial vesicle	+ve: IgA,Ig6,C3 along B.M.Z.
2	M	50	1 yr	blisters:mouth	No	none	sub-epithelial vesicle	-ve
3	F	58	3 yrs	blisters:mouth	No	larynx,pharynx:eyes	non diagnostic	-ve
4	F	63	9 mnths	desquamative gingivitis	Yes	eyes	sub-epithelial vesicle	-ve
5	F	67	5 yrs	blisters:mouth	Yes	eyes	sub-epithelial vesicle	+ve:C3 along B.M.Z.
6	F	18	4 yrs	desquamative gingivitis	Yes	skin,eyes,vagina	sub-epithelial vesicle	-ve
7	F	66	6 mnths	blisters:mouth	No	skin	sub-epithelial vesicle	-ve
8	M	55	5 mnths	conjunctivitis	No	mouth,nasal mucosa	sub-epithelial vesicle	-ve
9	M	67	6 mnths	blisters:mouth	No	scalp	non diagnostic	not done
10	F	35	1 mnth	blisters:mouth, desquamative gingivitis	Yes	skin, eyes,pharynx	sub-epithelial vesicle	+ve:C3 along B.M.Z.
11	M	53	1 yr	blisters:mouth	Yes	none	sub-epithelial vesicle	+ve:C3 along B.M.Z.
12	F	63	3 yrs	blisters:mouth desquamative gingivitis	Yes	none	sub-epithelial vesicle	+ve:C3 along B.M.Z.
13	F	68	10 yrs	blisters:mouth	Yes	none	sub-epithelial vesicle	+ve:C3 along B.M.Z.
14	M	68	1 yr	blisters:mouth	No	nasal mucosa pharynx,skin	sub-epithelial vesicle	+ve:C3 along B.M.Z.

* +ve = direct immunofluorescence positive
-ve = direct immunofluorescence negative
BMZ - basement membrane zone

4. Duration of Symptoms before Diagnosis

The time lapse between the onset of symptoms and the establishment of a definitive diagnosis ranged from one month (patient No. 10) to up to ten years (patients No. 1 and No. 13). The average lapse of time was quite long at two years and nine months. Nine of the fourteen patients remained undiagnosed for one year or more.

5. Initial Complaint

Of the fourteen patients, eleven stated that their initial symptom consisted of an outbreak of blisters in the mouth. Subsequently these ruptured and ulceration occurred and in most cases spontaneous healing eventually occurred. One patient(No. 1) reported the concurrent development of conjunctival blisters. Four patients (No. 4,6,10,12) complained of sore, bleeding and ulcerated gums as their first or concurrent initial symptom. Conjunctivitis by itself was the presenting complaint in only one patient (No. 8). Despite the often observed severe oral ulceration suffered by these patients, pain was not often a major complaint.

6. Clinical Findings

Intact intra-oral bullae were observed in seven patients. In five patients the bullae were seen either on the soft palate or towards the posterior border of the hard palate; a fifth patient had a bulla on the posterior region of the lower edentulous alveolar ridge, a sixth patient developed a bulla on the buccal

mucosa, and the seventh developed bullae in different locations at various times. All these lesions had a characteristic thick-roofed, tense appearance and were filled with either a clear or blood-stained fluid. They were usually seen to occur singly but in one patient (No. 4) six vesicles were observed clustered together on the right side of the soft palate. The size of these lesions ranged from 2 mm up to 1 cm. In one patient (No. 5) a bulla was observed on the soft palate over a period of four days, gradually increasing in size to 5 mm before rupturing.

Oral ulceration in varying degrees of severity was present in all of the patients. The ulcerated areas had a characteristic appearance. Rather than being cratered (as a true ulcer) they were covered with degenerating epithelium (presumably the roof of the bulla) which could easily be peeled back to expose the underlying connective tissue base. The sites most commonly affected by ulceration were the hard and soft palates, the buccal mucosa, gingiva or alveolar ridges, and the lateral and ventral surfaces of the tongue.

Some of the patients also exhibited fine lacy white striae on the oral mucosa - particularly the cheeks - which resembled those seen in non-erosive lichen planus, but these were interpreted as being residual scars from where previous lesions had healed.

Ten patients subsequently developed lesions elsewhere on the body. The most commonly affected secondary site, seen in six cases was the conjunctiva. Conjunctivitis of varying severity was the most common lesion and no vesiculation was ever observed. In all cases the eyes were involved bilaterally. In some of these

patients active conjunctivitis was not always present. Despite this there was evidence of scar tissue in the eyes of all six patients. These changes were most commonly seen to affect the lower conjunctiva towards the inner canthus of the eye. Quite severe ocular disturbances had occurred in patient No. 1 in whom the scarring was so severe as to have caused marked symblepharon, ankyloblepharon, and entropion. Four female patients reported in fact that their eye lashes had begun to grow inwards and subsequently to fall out.

The next most commonly affected site was the skin. Of the five patients reporting skin lesions, three (No. 1,6,10) stated that actual blisters had occurred. In patient No. 1 they were confined to the face and particularly the nose; in patient No. 6 an episode of extensive leg blisters was reported; in patient No. 10 blisters had affected the lower abdomen, groin, axilla and upper legs.

In all of these patients, except patient No. 1, the lesions had healed completely with no evidence of scarring. The lesions on the nose of patient No. 1 had remained as indolent, scaly, erythematous areas. Patient No. 7 reported a self-limited erythematous rash on her back which she stated was extremely itchy. Patient No. 14 had had for some time an indolent ulcerative lesion on the dorsal surface of his left forearm which resisted all measures aimed at its healing.

The pharynx was affected in two cases (No. 3 and 10). Pharyngeal involvement in these patients was manifested by a dry sore throat and some degree of dysphagia. Where the larynx had

been affected the voice had become quite hoarse. In patient No. 3, 75 percent of the larynx had been removed to correct a chronic laryngeal stridor.

Other sites involved were the nasal mucosa, scalp and vaginal mucosa. In patient No. 8 there had been several reported episodes of some spontaneous slight nasal bleeding. The scalp in the temporal region of patient No. 9 showed several erythematous crusted plaques. Patient No. 6 had developed quite severe vulval and vaginal lesions.

7. Diagnosis

An incisional or excisional biopsy (in the case of intact bullae) was performed for all patients. Sections were stained with haemotoxylin and eosin and examined by light microscopy. In twelve cases a definite subepithelial cleft was observed. The remaining two cases (No. 3 and 9) failed to reveal tissue changes of any diagnostic value.

Thirteen of the biopsy specimens were also examined by direct immunofluorescence. Seven of these specimens showed positive results. Only one specimen (No. 1) gave a positive result for patchy linear deposits of IgA and IgG along the basement membrane. All seven specimens, however, showed patchy granular deposits of C3 in the region of the basement membrane.

It is interesting to note that of the seven intact bullae biopsied and examined by direct immunofluorescence, five showed positive findings. Only two biopsy specimens taken from recently ruptured vesicles demonstrated positive direct immunofluorescence.

VI THE COEXISTENCE OF PEMPHIGOID AND OTHER DISEASES

1. Pemphigoid and Malignancy

2. Associated Diseases and Autoimmune Phenomena

3. Photo-Induction of Lesions

VI THE COEXISTENCE OF PEMPHIGOID AND OTHER DISEASES

Introduction

For many years the literature has contained a significant number of reports of patients suffering from pemphigoid and another disease entity, some autoimmune in nature.

The spectrum of autoimmune diseases can be seen to range from "organ specific" conditions at one end, to "non organ specific" conditions at the other. (Table IV.1) In simple terms the former category implies that autoantibodies are specific for one tissue type, whereas in the latter category neither autoantibodies nor lesions are confined to any one organ.

Patients with autoimmune disorders are prone to developing other diseases in the same region of the autoimmune spectrum, and, as will be discussed in a later section, some of these conditions have been reported in patients with a coexistent pemphigoid eruption. Still further, there have been a significant number of reports of patients in which malignancies were present and who subsequently developed a pemphigoid eruption.

Difference of opinion occurs as to whether there is an actual causal relationship between pemphigoid and these other diseases (particularly those of the autoimmune variety). On the other hand these coexistences may be due to the fact that most patients with pemhigoid are elderly and are hence more likely to be suffering from an autoimmune disease or a malignancy.

1. Pemphigoid and Malignancy

(i) Introduction

The human integument (skin and mucosa) has been shown for many years to mirror a large number of internal (sometimes occult) disorders.[46] It has also been long recognized that the development of a malignant neoplasia in an internal organ may be accompanied thereafter by the manifestation of certain types of skin diseases.[22] Indeed it was as early as 1890 that Pollitzer described acanthosis nigricans as a complex of symptoms which accompanied carcinoma of the stomach.[46]

The internal malignancies may be accompanied by various types of skin manifestations due to actual invasion of the skin by the malignancy and also by a remarkably diversified group of skin reactions in which the malignancy cannot be identified.[46] Thus cutaneous manifestations associated with malignant tumours may be categorized as specific or non-specific lesions.[191] The specific lesions display the typical histology of the basic disease and include mainly papules, nodules, infiltrations and occasionally exfoliative dermatitis. These lesions are especially seen in leukaemias and in malignant lymphomas. The non-specific lesions are of widely variant types but are most commonly haemorrhagic skin lesions and pruritus. However, not infrequently vesiculo-bullous eruptions occur such as those of pemphigus and pemphigoid.

(ii) Oral Manifestations in the Paraneoplastic Syndrome

In the early 1950's the paraneoplastic syndrome was recognised as a disease entity in its own right. The paraneoplastic syndrome is a complex of symptoms which is not a form of metastasis but is associated with a malignant tumour in an internal organ or with a malignant system disease.(22) The manifestations will disappear without any additional treatment after a cure or a removal has been effected of the "primary" tumour. These manifestations will, however, reappear if and when the tumour recurs. Moreover, these manifestations show no histological similarity or analogy to the primary malignancy. Perhaps the most essential feature is that, within the complex framework of this pathological process, the malignant neoplasm is the first to develop. It is difficult to describe the exact mechanism by which different forms of the paraneoplastic syndrome occur; suffice to say that the same malignancy in different patients may cause different cutaneous and/or oral manifestations. Accordingly, the oral manifestations of the paraneoplastic syndrome may appear in various forms depending upon the predominance of autoimmune, allergic, and/or toxic symptoms, the type of primary malignancy and the organ in which it occurs.

The possibility of a causal relationship existing between vesiculo-bullous diseases and malignant neoplasia remains the subject of great controversy. Pemphigoid has been called a typical paraneoplastic vesicular manifestation(22) and Wilson,(64) Hellier(64) and Gold(128) believe that a causal relationship exists, particularly in cases where severe oral mucosal involvement

occurs.

No undeniable proof of a causal relationship between pemphigoid and internal malignancy has yet been forthcoming in the literature. However, if paraneoplastic syndrome is suspected in a patient with pemphigoid it is perhaps prudent, if only for the patient's well-being, that a thorough medical examination be carried out to exclude the presence of a malignancy. If a primary malignancy is not found then one is not justified in speaking of a paraneoplastic syndrome. This term should also only be used as a possible pathomechanism and not as a diagnosis.

(iii)Review of the Literature

Reports of patients developing bullous pemphigoid whilst suffering from an internal malignancy are not uncommon in the dermatological literature. However, there is a noticeably smaller number of cases reported in which the vesiculo-bullous eruption, developing in patients with a malignant neoplasm, has been described and diagnosed as that of cicatricial pemphigoid. This deficiency is perhaps difficult to understand in the light of the observation made by several authors that when a subepidermal blistering eruption does occur in a patient with a malignancy then the oral lesions are more likely to be quite severe.[23,128,152,175,195] The smaller number of cases reported concerning cicatricial pemphigoid as opposed to bullous pemphigoid developing in patients with malignancy may be due to several factors. Primarily this may be due to the much larger proportion of cases of bullous pemphigoid reported in the literature. Secondly, and perhaps accounting for

the first explanation, is the fact that dermal lesions are far more likely to be reported by a patient and hence diagnosed. Cicatricial pemphigoid as it affects the oral mucosa is much less accessible to diagnosis and far less specific in the appearance of its lesions than is bullous pemphigoid. By far the greatest number of cases of either type of pemphigoid have been reported by dermatologists. Finally, perhaps the simplest reason is that cicatricial pemphigoid, despite being almost certainly a variant of bullous pemphigoid, does not in fact occur as often in patients with a malignancy as does bullous pemphigoid.

A review of the literature concerning patients who developed cicatricial pemphigoid whilst suffering from a malignant neoplasia is presented in Table VI.

Analysis of this table, as regards age, sex, and type of malignancy, reveals no significant findings albeit the small numbers of cases involved.

The average age of patients in this review was 55 years. This figure is not significant as most patients who develop cicatricial pemphigoid and indeed a malignancy are most commonly middle aged to elderly. Twice as many females as males are seen in this review. This cannot be considered a sex prediliction for pemphigoid occurring in patients with a malignancy because it is undisputed that approximately twice as many patients suffering from cicatricial pemphigoid will be females. Again no particular organ affected by malignancy nor any one type of malignancy predominated in this review.

TABLE VI CASES OF CICATRICIAL PEMPHIGOID AND ASSOCIATED MALIGNANT DISEASE REPORTED IN THE LITERATURE

SOURCE	AGE/SEX	TYPE OF MALIGNANCY	PARALLEL COURSE
Bohatka et Alfoddy(22)	52/F	Ca breast	Yes
Parsons	38/F	Ca lung	Yes
et Savin(152)	77/F	Lymphosarcoma	Yes
Boyd(23)	76/F	Ca pancreas	Pt. died
Mark(128)	61/F	Melanoma	Yes
Saikia, Mackie et McQueen(175)	48/M	Adenocarcinoma Rectum	Yes
Chadfield et	47/M	Bronchogenic Ca	Pt. died
Kanagasundaram(38)	56/M	Basal cell Ca	Pt. died
Jamieson(95)	40/M	S.C.C. palate	Pt. died
Polliack(163)	49/F	Adenocarcinoma thyroid	Pt. died
Mitchell et	65/F	Adenocarcinoma bowel	No
Smith(138)	55/F	Unknown	No

The findings of Stone and Schroeter[198] are also in accordance with this review. They examined seventy-three patients with pemphigoid. Each patient was matched by age, sex, and calendar year of diagnosis with two other patients - one with psoriasis and one with contact dermatitis. Of the seventy-three patients, eight were determined to have a systemic malignant disease. Ten of the psoriatics and eleven of the patients with contact dermatitis also had malignancies. Their findings showed no sex predilection for neoplasms. The distribution by age and sex was also not significant. It was also apparent that the types of cancers found in these patients were not distinctive.

(iv) Cicatricial Pemphigoid and Malignancy - A Parallel Course ?

Several authors have noted that the progress of the malignancy and the lesions of the coexistent cicatricial pemphigoid may run a parallel course.[22,128,152,175,191] This refers to the fact that the pemphigoid lesions would disappear when the primary malignant tumour was surgically ablated and yet if the turmour returned per metastatic disease, then the pemphigoid lesions returned and persisted until the patient's eventual demise. In fact the severity of the oral mucosal pemphigoid lesions became more severe as the malignancy progressed. Skog[191] believes that the only definite criterion that pemphigoid lesions are actually caused by the malignant tumour is that if the tumour is wholly or partly removed then the bullae either disappear or become milder. Chadfield and Kanagasundaram[38] believe that the coexistence of

the two conditions accelerates the neoplastic process and that cicatricial pemphigoid not only predisposes to malignant disease but also introduces some factor which may accelerate the malignant process. No pathomechanism is suggested to substantiate these hypothoses.

It would appear, from the cases reported in the literature, that if oral lesions of cicatricial pemphigoid occur, recur or become more severe in a patient who is known to have had a malignant neoplasm removed then a thorough physical examination should ensue to discount the possible development of metastatic malignant disease.

(v) Mechanisms of Blister Formation in Patients with Malignancy

The pathomechanisms involved in the formation of vesicles and bullae in patients with malignant neoplasms is not known, although several hypotheses have been expounded.

Several authors[116,124,140] have noted that pemphigoid eruptions (usually dermal) may develop following a course of radiotherapy for malignant disease. Cormia and Domonkos[46] suggest that the bullae may have been produced by the breakdown products of the tumour, although they do not suppose as to what these breakdown products might be or how they induce a pemphigoid lesion.

Malignant neoplasms could secrete a hormone-like substance that might produce damage to the epithelial basement membrane zone. Antibody to the basement membrane area might then be formed secondarily.[53]

Much less likely, a virus or other agent might induce a malignant neoplasm and simultaneous basement membrane zone damage.

As has been discussed previously, cicatricial pemphigoid is associated with circulating and tissue bound IgG antibody that binds to the basement membrane zone of various epithelial tissues. These antibodies are capable of fixing complement and inducing tissue damage leading to the formation of a subepithelial vesicle. It is also known that persons with malignant tumours mount an immune response directed against tumour-specific antigens on malignant cells. If malignant tumours can in fact produce an eruption of cicatricial pemphigoid then an immunological mechanism would seem likely.(53)

Theoretically, antibody formed against tumour antigens might cross react with antigens in the basement membrane zone of squamous epithelium. These cross reacting antibodies might fix complement at the basement membrane and induce vesicle formation. If antibodies formed against tumour cells and cross reacted with epithelial basement membrane then it would be possible to absorb antibasement membrane antibodies with tumour cells. Unfortunately, no such cross-reactivity has been yet demonstrated.

It seems prudent at this stage, in the light of all the preceding observations, to regard cicatricial pemphigoid as merely a chronic disease of the elderly that may from time to time be seen to occur in patients with a malignant (or benign) tumour. There is little evidence to suggest that the two conditions bear any causal relationship to one another or that an intensive search for an underlying malignancy is indicated except perhaps, as previously

stated, in those patients who demonstrate a recurrence of severe oral lesions sometime after having had a malignant tumour removed.

(vi) Cicatricial Pemphigoid and Oral Squamous Cell Carcinoma

Chronic local irritation is of paramount importance in the development of oral squamous cell carcinoma and is most often associated with chronic alcohol intake and cigarette smoking. Certain pathological conditions, particularly those manifesting themselves as leukoplakic lesions, have received considerable attention as being premalignant. One such condition is lichen planus.

Despite the obvious chronicity of a condition such as cicatricial pemphigoid which will produce, after a time, large ulcers, little attention has been given to the possible role a chronic bullous disease such as cicatricial pemphigoid might play in the development of oral squamous cell carcinoma.

It has been suggested that oral squamous cell carcinoma may become a more prominent feature of the chronic vesiculo-bullous diseases since patients are now being observed for longer periods and in the case of those suffering from pemphigus, are being kept alive longer with corticosteroid and immunusuppressive therapy.[62] Despite this prediction only two cases of cicatricial pemphigoid have been reported in which oral squamous cell carcinoma developed.[62,95] In the patient reported by Jamieson[95] a squamous cell carcinoma was shown histologically to be present in a lesion that also showed microscopic changes characteristic of cicatricial pemphigoid. This malignant lesion developed in the

anterior hard palate - an area regarded as somewhat "immune" to the development of squamous cell carcinoma - and in the absence of any other stated aetiological factors, some validity may be attached to the precept that the long standing lesions of cicatricial pemphigoid present in this position for some seven years predisposed the mucosa to developing malignant change. Faraci, Schour and Graykowski[62] described field carcinomatous change occurring in the tongue and oropharynx of a patient who had suffered from untreated cicatricial pemphigoid (involving the tongue) for some five years. In this case again no aetiological factors commonly associated with the development of squamous cell carcinoma were shown to have been present.

As has been stated these two cases are unique in that a carcinoma actually developed within long standing lesions of untreated cicatricial pemphigoid in the absence of any aetiological factors associated with malignant transformation of oral mucosa. Long standing chronic irritation may have been an initiating factor although it would be difficult to state definitely, in the light of only two cases, that long standing cicatricial pemphigoid predisposes the oral mucous membrane to the development of squamous cell carcinoma.

2. Associated Diseases and Autoimmune Phenomena Seen in Pemphigoid.

There have been sporadic reports in the literature of patients with an existent pemphigoid eruption developing another disease. Interest has been aroused when these other diseases have proven

to be autoimmune in nature. Unfortunately no attempt has been made to explain the possible pathomechanisms involved in the coexistence of pemphigoid and these other autoimmune diseases.

Bullous pemphigoid has been reported in association with rheumatoid arthritis,[119,158,176,216] systemic lupus erythematosus,[101] polymyositis,[155] pemphigus vulgaris,[41,158] pemphigus foliaceus,[78] chronic pancreatitis with hypothermia,[193] pernicious anaemia,[150] chronic renal failure,[157] polymyalgia rheumatica and thyroid disease,[89] alopecia areata,[158] hypothyroidism,[158] toxic goitre,[158] and inflammatory bowel disease.[158]

Still fewer reports have appeared in the literature of patients suffering from cicatricial pemphigoid and another autoimmune disease. Schreiber[180] described a fifty-one year old male from whom an intact buccal mucosal vesicle was biopsied. The histopathological and immunopathological picture confirmed a diagnosis of cicatricial pemphigoid. Culture of the vesicle fluid, however, grew herpes simplex virus. A similar case was reported by Walker[216] of a patient who suffered from bullous pemphigoid and rheumatoid arthritis - again the vesicular fluid contained herpes simplex virus.

Personé and Rogers[158] reported on sixty-three patients with diagnosed cicatricial pemphigoid. Of these patients, fourteen demonstrated the concurrence of another disorder, some of which were autoimmune in nature. These phenomena included positive nuclear antibody, rheumatoid arthritis, positive smooth muscle antibody, hypothyroidism, toxic multinodular goitre and inflammatory

bowel disease.

(i) Pathomechanism for the Appearance of an Associated Disease and Pemphigoid

As has been stated, very little attempt has been made to investigate the possible pathomechanisms involved in the development of associated diseases in patients suffering from pemphigoid. The hyoptheses propagated have been purely speculative. Salo and Rasanen[176] found that 22 percent of their patients with pemphigoid also suffered from rheumatoid arthritis. They suggested that this figure was high enough to suggest a definite association between the two disease processes. They also stated that in all their cases the rheumatoid arthritis had begun years before the bullous eruption. It is true that the incidence of rheumatoid arthritis in the population is much higher than that of pemphigoid. If there is in fact a relationship between these two conditions, then surely pemphigoid would appear much more commonly in patients who suffered from rheumatoid arthritis.

Two possible explanations may account for the apparent coexistence of pemphigoid and another disease entity (particularly those that are autoimmune in nature). It may be that an underlying immunological disturbance may give rise to one, two or even multiple types of autoimmune responses. In other words, antibodies produced in one disease process may be cross-reactive with antigenic determinants in another site, hence producing the second disease. This may be so in cases of pemphigoid occurring with the "similar" disease processes of pemphigus, systemic lupus erythematosus and

herpes simplex.

An alternative explanation would suggest that the only common denominator within this group of patients is their advanced age. The vast majority of patients who suffer from pemphigoid are middle aged and older. It would therefore be reasonable to suggest that elderly patients are much more prone to developing autoimmune diseases due to an age related breakdown in the immune system. Hence it would not be surprising to find a number of patients who suffered from two or more autoimmune diseases. As the number of patients reported to be suffering from pemphigoid and another autoimmune disease is quite small in comparison to the total number of patients reported suffering from pemphigoid alone, it would appear that any such relationship may well be purely coincidental.

(ii) Drug Induced Pemphigoid Eruptions

It has been understood for many years that a great array of therapeutic preparations have a variety of untoward side effects. Not uncommon amongst these side effects are a number of muco-cutaneous disorders, some of which may mimic or in fact be auto-immune diseases. Of the autoimmune disorders, the pemphigoids have been reported to develop in association with various drug therapies.

The prerequisite that any disease has been induced by a therapeutic agent must be that the disorder disappears some reasonable time after the withdrawal of the drug in the absence of any other therapeutic action taken against the disease.

Several drugs have been implicated as the causative agents for the development of pemphigoid eruptions in patients taking these medications. The list of drugs is small but includes D-penicillamine,[22,156] practolol,[98] clonidine,[99] echothiophate iodide,[153] epinephrine,[6,105,149] and azaproprazone.[7]

(ii(a) D-Penicillamine

The drug D-penicillamine (B_1B_2 dimethylcysteine) may be prescribed for the therapeutic management of a number of diseases because of its multiple pharmacological actions. It is the drug of choice in Wilson's disease, may also be used in some heavy-metal intoxications, and also is suitable for the treatment of cystinuria. It is also of benefit in cases of rheumatoid arthritis.[22]

The use of D-penicillamine is not without clinical problems. Up to fifty percent of patients develop sensitivity-type reactions which may present as fever, joint pain, lymphadenopathy, or skin eruptions that range from a maculopapular itchy rash to a severe dermatitis. Bone marrow suppression can also be a problem.

These initial reactions are different from another group which occur after relatively high dose therapy has continued for some time, and which are caused by the apparent ability of D-penicillamine to induce autoimmune disorders.

Pegrum and Pembroke[156] reported a case in which cicatricial pemphigoid appeared in a man taking D-penicillamine for two years for treatment of rheumatoid arthritis. Despite withdrawal of the drug the pemphigoid lesions remained extant for nine months. During

this period he was treated with prednisolone and azathioprine which was seen to be remarkably successful. As oral ulceration (which was this patient's original symptom) is a recognized side effect of D-penicillamine therapy, the authors pondered the possibility that some cases of D-penicillamine induced mouth ulcers are formes frustes of cicatricial pemphigoid. They also noted that the lesions of cicatricial pemphigoid failed to respond to cessation of the drug.

The reason for persistence of the lesions after cessation of D-penicillamine, and the need for additional therapy might be found in the suggestion made by Hay, Muller and Reade.[80] D-penicillamine could act as a hapten, with the consequent stimulation of immune responses against tissues to which the drug had bound. This would explain the variety of autoimmune-like side effects, including cicatricial pemphigoid, and the prolongation of symptoms beyond the time of withdrawal of the drug. D-penicillamine might also exert its autoimmune-like effects by a direct action on lymphocytes, thereby altering their behaviour in a variety of functions. Neither of these propositions, however, has support from experimental evidence, so that the mechanism whereby D-penicillamine causes the side effects described remains unknown.

(ii)(b) Clonidine

Clonidine is a well known α-adrenergic receptor stimulating agent. Van Joost, Faber, and Manuel[99] reported a case of cicatricial pemphigoid affecting mucosal surfaces of the anus and

the vulva, associated with long term therapy with clonidine.

The lesions in this patient persisted for six months after withdrawal of the clonidine and despite the use of betamethasone 17-valerate. The reappearance of pemphigoid lesions after re-expsure to the clonidine was considered highly suggestive of a relationship between the use of the drug and the earlier development of an autoimmune syndrome with features of cicatricial pemphigoid.

This sequence of events is similar to that described by Hay, Muller and Reade[80] and by Pegrum and Pembroke.[156] However, a different underlying pathomechanism of side effects in patients using α-adrenergic receptor stimulating agents has been postulated. In 1976 van Joost, Crone and Overdijk described a case of ocular cicatricial pemphigoid apparently due to the long term use of the β-adrenergic receptor blocking agent practolol.[98] It has been hypothesized that β-adrenergic receptor blocking agents may interfere with the cyclic AMP system of epithelial basal cells.[98] In view of the concept that the basement membrane zone is in part of epithelial origin, then local metabolic disturbances in the cyclic AMP system of basal germinal cells might lead to the deposition of immunogens at the site of the basement membrane zone and subsequently to immune complex formation at this site. It may be that like β-adrenergic receptor blocking agents, α-adrenergic stimulating agents may cause similar alterations in the function of basal germinal cells of epithelium.

(ii)(c) Echothiophate Iodide and Epinephrine

Both echothiophate iodide and epinephrine when used topically are useful therapeutic agents in the control of glaucoma.

In 1974 Kristensen and Norn[6,105,149] examined the eyes of twenty-nine patients who were suffering from ocular pemphigoid. Of these patients, fourteen had had epinephrine drops instilled for some length of time before the signs of ocular pemphigoid developed. They concluded that the use of topically applied epinephrine might contribute to the development of ocular pemphigoid. However, no attempt was made at explaining the possible underlying pathomechanisms involved.

Patten, Cavanagh, and Allansmith[153] described two cases of ocular pseudopemphigoid(as they termed it) in patients who had received long term antiglaucomatous medication with echothiophate iodide. In both these patients the lesions of ocular pemphigoid only occurred unilaterally and only in the eye being treated for glaucoma with echothiophate iodide. Of interest also is the fact that one of these patients had previously received treatment for his glaucoma with epinephrine drops.

Biopsy specimens from both the affected and unaffected eyes of these patients showed an expected increase in the amount of inflammation (greater numbers of plasma cells). Echothiophate iodide and other autonomic drugs increase cholinergic action and are associated with increased inflammation through elevation of cyclic guanidine monophosphate. This may therefore suggest a relationship between echothiophate iodide, cholinergically induced inflammation, and induced ocular pemphigoid.

Alternatively, echothiophate iodide may slowly injure the conjunctiva through toxic mechanisms (perhaps iodide related) as in chemical or thermal injury.

No experimental evidence has as yet been presented to either accept or reject this immune - or toxic - initiated injury as the cause for apparently drug induced ocular cicatricial pemphigoid.

3. Photo-Induction of Lesions in Patients with Pemphigoid

Ultraviolet light can be an aggravating factor in some patients with pemphigus foliaceus and may result in extension of the disease to previously uninvolved skin.[47] The typical microscopic lesion appears between eighteen and twenty-four hours in the ultraviolet irradiated skin. Patients under intensive steroid therapy or with disease in remission fail to demonstrate a similar phenomenon. Ultraviolet light is a specific energy source and the most effective spectrum for induction of lesions would appear to be in the sunburn range.

Cram and Fukuyama[48] have also determined that application of ultraviolet light to the normal appearing skin of patients with bullous pemphigoid prior to the commencement of therapy can produce new lesions in the irradiated sites. Leading up to the development of histological changes is a sequential increase in the in-vivo binding of IgG and complement. This suggests that the pathogenic mechanism involved in the production of skin lesions following ultraviolet light is that of a progressive immunological reaction.

It would appear difficult to associate the results of the above studies to patients with cicatricial pemphigoid. However,

an analogy may be drawn in considering the group of patients who suffer from that type of cicatricial pemphigoid as described originally by Brunsting and Perry.[30] They described lesions of pemphigoid associated with scarring, usually occurring in sun-exposed areas in males.

The induction of pemphigoid lesions by ultraviolet light may also explain those instances of transient lesions of pemphigoid occurring in patients suffering from psoriasis.[2,157,158] One method of treating patients suffering from psoriasis is to expose them to ultraviolet radiation therapy (in the sunburn range).

Cram[47] has attempted to explain the mechanisms by which the binding of IgG and complement are initiated in the skin of patients with pemphigoid following exposure to ultraviolet irradiation. Several factors may be involved individually or collectively.

The effect of ultraviolet light may be to produce an increased concentration of both IgG and complement in the epidermis by possible destructive effects on the basement membrane zone, thus producing the threshhold levels of IgG and complement required for the evolution of frank pathological changes.

Ultraviolet light is known to cause DNA to become immunogenic.[205] Conceivably, ultraviolet irradiation of uninvolved skin of patients with pemphigoid could result in the release or activation of bound antigen and/or promote antibody fixation leading to the appearance of specific pathology. In other words, ultraviolet light may have a more direct effect on the epithelium and in some way antigenically change the in-vivo reactivity at the site of pathological change.

As already stated, ultraviolet light does not induce pathological changes in the normal skin of patients undergoing active therapy for pemphigoid. This knowledge may thus be useful in assessing the effects of systemic corticosteroids and other immunosuppressive drugs on the skin of patients suffering from pemphigoid.

Ultraviolet light irradiation may also prove to be a useful procedure in helping to confirm the diagnosis of pemphigoid in patients whose skin lesions are not diagnostic clinically or histologically, by reproducing fresh, characteristic lesions.

VII TREATMENT AND PROGNOSIS OF CICATRICIAL PEMPHIGOID

1. Local Measures
2. Topical Measures
3. Systemic Measures
4. Surgical Measures
5. Treatment of Ocular Lesions
6. Prognosis

VII TREATMENT AND PROGNOSIS OF CICATRICIAL PEMPHIGOID

Introduction

Since the aetiology of cicatricial pemphigoid remains essentially unknown, no specific curative therapy is available. However, as with many other such diseases, a number of therapeutic measures may be employed to control the pathological process and hence give complete or partial relief of the symptoms.

It should be made clear to all patients at the outset that the aim of treatment is control of the pathological process rather than an effective cure of their disease. Successful management of patients with cicatricial pemphigoid in a large number of cases does not entirely rest within the realm of the dental profession. These patients should be under the combined care of qualified medical specialists such as clinical immunologists, physicians, ophthalmologists, otolaryngologists, and nutritionalists.

Treatment should be on an individual care basis and may include local, topical, systemic, or surgical considerations, which vary depending upon the site of involvement and severity. The most pressing need in treatment is the arrest of progressive ocular, oesophageal and laryngeal scarring to prevent blindness, cachexia and chronic laryngeal stridor.

1. Local Measures

In the case of oral lesions the dental surgeon is best equipped to deal with the elimination as far as possible of

irritating factors such as trauma, bacteria, or chemicals. Proper care of the teeth, gingivae, and prostheses(when present) should be the primary aim of the dentist.

(i) Care of the Dentition and Periodontium

It is most essential that patients with oral lesions of cicatricial pemphigoid retain as many of their natural teeth for as long as is feasibly possible. This should avoid the necessity for the patient to wear dentures as they are always a problem as far as trauma to the oral mucosa is concerned.

The patient will in all probability be discouraged from maintaining the required high level of oral hygiene because pain (particularly during active phases of the disease) on brushing the teeth may be a troublesome problem - mucosal lesions (particularly gingival) may be easily traumatized by a toothbrush and the flavouring agents in toothpastes may be highly irritating. It is therefore not unusual initially to see a poor level of oral hygiene in patients with severe oral lesions. (Fig.VII.1)

In these cases irritating agents such as the toothbrush and toothpaste should be discarded until the oral lesions are rendered quiescent by other therapeutic agents. During this period the dental surgeon should endeavour to eradicate plaque and calculus and to reduce any periodontal pocketing. Zamet[224] suggested that the mouth be treated in four quadrants under a local anaesthetic, thus allowing time for healing in each area before proceeding to the next. His technique involved the removal of all soft friable gingival tissue in an attempt to eliminate pocket

Fig.VII.1.Very poor oral hygiene has been a consequence of great discomfort during toothbrushing. A natural progression to a severe periodontitis has occurred. (Patient 1. TableV)

depths and restore gingival contour. At the same time the teeth were scaled and the root surfaces planed smooth. A non-eugenol periodontal pack was applied for one week, then redressed for a further week.

Several important features of this treatment regimen arise. This method of treatment should only be undertaken when the patient is on a maintenance drug dosage. However, if the patient is receiving systemic corticosteroid therapy then the dosage should be increased twenty-four hours prior to periodontal surgery to prevent the systemic disease from interfering with wound healing and to avoid the possibility of an adrenocorticotrophic crisis. Secondly, oral administration of an antibiotic is necessary to guard against possible infection.

Following the initial measures conducted by the dental surgeon, oral hygiene should be taught. If a toothbrush can be used then it must be soft and multitufted. Zamet[224] noticed that the use of an electric toothbrush produced dramatic changes in oral cleanliness. An alternative to the toothbrush is a device producing a pulsatile water lavage which, despite being less effective, may be satisfactory if trauma from a toothbrush is a problem. A bland fluoridated toothpaste is also a desirable adjunct. The careful use of interdental wooden sticks or dental floss is necessary to maintain an adequately high level of periodontal health.

If pain remains a barrier to the maintenance of oral hygiene by the patient then the use of a topical anaesthetic mouthwash immediately prior to toothbrushing should be of great benefit,

but may carry the risk of tissue trauma due to over enthusiastic brushing.

(ii) Prosthetic Management

As has been stated, denture prostheses are always a problem, because they are an obvious source of trauma, of which the slightest amount may elicit vesicle formation.

The painful oral condition which occurs during active phases of the disease results usually in a lack of oral hygiene, which in turn increases the need for prosthetic services in these patients. Additionally, as most of thepatients who suffer from cicatricial pemphigoid are elderly there is an increased need for prosthetic management. These patients can be treated most successfully in the dental surgery if there is a strict adherence to modern prosthodontic principles.

In all procedures during construction of dentures standard clinical techniques may be used although it is mandatory that the oral tissues be gently manipulated because of the compromised nature of the epithelium.

The important clinical considerations are that the denture be smooth, highly polished, and stable so as to avoid the risk of mechanical irritation to the mucosa.[211] Careful attention should also be paid to occlusal harmony and smooth rounded flanges which have been moulded precisely. These features if carefully attended to will increase the stability of the denture.

It is the view of some authors[132,187] that soft tissue conditioners may be sometimes of great value to denture wearers,

particularly during active phases of the diseases. They may help to cushion the denture on the soft tissues and hence reduce mechanical irritation. Tolentino,[211] however, is not convinced that successful prosthetic treatment of these patients necessitates the use of soft liner materials. He based his decision to use soft tissue lining materials solely on the fact that there would be fewer problems for patients in the undercut regions, particularly of the maxilla. The use of soft tissue liners in this situation is commendable as it will reduce the need for avoidable pre-prosthetic surgery.

There is no question that the patient should be recalled to the dental surgery on a regular basis in order that the fit and stability of the denture may be re-assessed and any corrective procedures carried out before tissue injury occurs.

It is generally accepted that patients with cicatricial pemphigoid should only wear their dentures when absolutely necessary to minimize tissue trauma. This is particularly so during active phases of the disease process. It may therefore seem contradictory to say that dentures may be of some benefit when using topical corticosteroid preparations on lesions of cicatricial pemphigoid that occur on denture bearing areas of the oral mucosa (see discussion on topical corticosteroids).

2. Topical Measures

Topical medication appears to be most helpful in the treatment of oral lesions of cicatricial pemphigoid. Before commencing any such treatment it is necessary to first eliminate

any "home therapy" such as irritating mouthwashes. In their place are substituted soothing preparations as a bland lavage to reduce inflammation. A 0.2 percent chlorhexidine mouthwash used under direction is a most satisfactory means of reducing the amount of secondary infection in oral lesions.[138]

(i) Topical Corticosteroids

Other more specific agents may be employed including topically administered corticosteroids. Direct application of corticosteroids to the target organ as a means of avoiding the unwanted effects of systemic treatment is now well known in many areas of medicine, and has probably been the major therapeutic advance in dermatology.[136] Despite the tremendous benefit topical corticosteroid preparations has brought to a large number of diseases, the success of their local application to oral lesions of cicatricial pemphigoid has been limited and unpredictable.[186] A very large range of topical corticosteroid preparations exists ranging from mild to very potent in their activity.[136] It is therefore wise to understand and follow certain guidelines when prescribing such medications.

(i)(a) Influence of Anatomical Site on Penetration

A large percentage (approximately ninety) of corticosteroid applied to normal forearm skin is wasted.[136] There is large variation in absorption between individuals and also between anatomical sites. The mucous membrane is an area of high penetrability and is an area which may tend to develop local side effects more easily. Here, therefore, the less potent corticosteroids

are more suitable.

It is felt that the barrier to absorption is the layer of keratin. This is obviously relevant in trying to assess penetration of a topical corticosteroid through diseased mucosa. In the ulcerative lesions of cicatricial pemphigoid, the epithelium is obviously atrophic or even completely absent. Hence the barrier to penetrability of the oral mucosa in a patient with cicatricial pemphigoid is markedly reduced and therefore a less potent corticosteroid preparation would be more suitable.

(i)(b) Influence of an Occlusive Dressing

The most effective way of increasing corticosteroid penetration is in fact to occlude the surface with an impermeable film. Penetrability may be increased by up to ten-fold. It would appear therefore that a patient's dentures or a treatment appliance may be of great use in treating pemphigoid lesions as they affect denture bearing areas. Applying a topical corticosteroid preparations to the tissue surface of a denture may well prove rewarding as they are afforded ample time for absorption and indeed may act as a cushioning agent for the appliance.

However, there would appear to be problems in occluding the oral mucosa with plastic. Occlusion may lead to an increased risk of bacterial and candidal infections and more importantly the resultant increased absorption may lead to an increased risk of local and systemic side effects. It is therefore generally advised to maintain plastic occlusion for no more than twelve hours daily. This is in accordance with regular denture hygiene.

Since even a few hours occlusion can lead to a measurable increase in penetration, relatively short periods of occlusion may be clinically useful and it may be beneficial to construct treatment appliances for those patients who are dentate (or who have no dentures).

In this light it would appear to be more beneficial to use a greasy ointment as a vehicle because of its increased occluding effect and also because it is less easily washed off the oral mucosa by saliva and mucus. Despite the lack of published research into the relative merits of creams as opposed to ointments,as regards their use on the oral mucosa, it has been found recently that topical corticosteroid creams may produce equally effective clinical results as well as being better tolerated by some patients.[97a]

(i)(c) Rationale for the Use of Topical Corticosteroids

The anti-inflammatory activity of corticosteroids, when present in pharmacological doses, is their main therapeutic property. This activity is nonspecific because it is exhibited against most of the causes of inflammation, whether mechanical, chemical, microbial or immunological. Corticosteroids may depress the formation, release and action of the endogenous chemical mediators of inflammation including the complement system.[136] This may well be of great importance to the treatment of cicatricial pemphigoid. Corticosteroids may also inhibit the migration of lymphocytes to the diseased site - another factor of significance in the treatment of cicatricial pemphigoid.

Corticosteroids also exert an immunosuppressive action by inhibiting the division of immature lymphoid cells and antibody production, although this action is manifested too slowly to explain the immediate effects on immunologically induced inflammation.

(i)(d) Corticosteroid/Antimicrobial Combinations

There are a number of preparations available which combine a corticosteroid with a broad spectrum antimicrobial agent. Combination therapy is probably superior in the treatment of secondarily infected conditions.

The oral environment contains a vast number and variety of commensal organisms. However, in a condition such as cicatricial pemphigoid where the oral mucosa may be severely ulcerated it is not uncommon to find that these lesions have become secondarily infected, and particularly by Candida albicans. It would therefore seem reasonable to recommend a combined corticosteroid/antimicrobial preparation for the treatment of the oral lesions of cicatricial pemphigoid unless bacteriology suggests otherwise. Perhaps even greater therapeutic results may be achieved by the separate use of these drugs on an individually tailored dosage.

(i)(e) Frequency of Application

Tachyphylaxis (decreased biological activity) may occur after long and repeated applications of a topical corticosteroid. Corticosteroids are also known to penetrate the human integument very slowly and may exhibit a reservoir effect.(136)

As a general rule, therefore, it would seem appropriate in the treatment of oral lesions of cicatricial pemphigoid that the topical corticosteroid be applied on a number of occasions during the day but only during active phases of the disease.

(i)(f) Local Side Effects

Several locally induced side effects of topical corticosteroid therapy may occur but are rare if the preparation is used correctly.[136]

Reversible epithelial thinning due to a positive dose-related reduction in cell size may occur with increasing concentrations of topical corticosteroid. The more potent corticosteroids have a marked inhibitory effect on fibroblast growth and lead to a decreased collagen content in connective tissue.

Increased ocular pressure, glaucoma, cataracts, and an increased risk of ocular mycotic infections and exacerbation of herpes simplex virus infections are unfortunately all complications of topical ocular corticosteroids. This poses a great problem in the treatment of the ocular lesions of cicatricial pemphigoid (see discussion on Treatment of Ocular Lesions).

The use of topical corticosteroids on healing areas may produce indolent ulcers. Hence the indications for the use of these compounds on healing ulcers of cicatricial pemphigoid would appear to be very few indeed.

(i)(g) Systemic Side Effects

Virtually all topical corticosteroid preparations will cause adrenal axis suppression if enough is absorbed and the compound is potent enough. Patients with liver failure and young children are more so at risk.(136)

Because cicatricial pemphigoid is in most cases a long term condition most patients will be using topical corticosteroids over a number of years. This behoves the attending clinician to regularly check the patient for possible adrenal axis suppression. This untoward effect is, however, unlikely except in the above situations or when the preparation is of high potency or being used incorrectly.

(i) (h) Treatment Guidelines

Many patients with cicatricial pemphigoid have benefited greatly from the use of topical corticosteroids. Obviously the aim is to produce the required clinical benefit with the least possible complications. Several guidelines concerning the use of topical corticosteroids can thus be drawn up:

1. Short courses of highly effective treatment which is then withdrawn until a relapse occurs seems preferable to prolonged treatment with a less active preparation. This should reduce side effects and possibly prevent lesions becoming refractory to treatment.

2. After the initial response, maintenance therapy (if needed) may be continued with the weakest preparation needed to control the lesions.

3. Combination corticosteroid/antimicrobial preparations should be used on lesions which are secondarily infected.

4. Occlusion by means of dentures or plastic treatment appliances may be of great benefit.

5. Corticosteroid preparations should be used with extreme care around the eyes.

6. The use of corticosteroids on healing ulcers should be avoided.

The actual technique of applying these agents to the lesions as they affect the oral mucosa may at first prove difficult for the patient. It is usually recommended that most success is attained by first thoroughly drying the affected field.(186) The patient should gently massage the agent into the inflamed area with the finger tip. It would appear that application to the affected area is best prescribed four times daily, after each meal and at bedtime for the best and most prolonged tissue contact.(132)

In Australia several topical corticosteroid ointments have been used in the treatment of the oral lesions of cicatricial pemphigoid. These include triamcinolone acetonide 0.1 percent, and betamethasone valerate 0.05 percent.

Recently, topically applied fluocinonide 0.05 percent was used in an adhesive base (Orabase) to treat patients at the University of California, San Francisco.(122) This is, like triamcinolone acetonide 0.1 percent, a potent topical corticosteroid. In this study the patients applied the ointment five or six times daily for two weeks and were instructed not to eat or drink for half an hour after application. The clinical

responses were excellent and adverse effects were essentially non-existent.

Of the combination corticosteroid/antimicrobial agents available in Australia the most commonly used include Pimafucort* (Hydrocortisone 10 mg/gm., neomycin 5 mg/gm., natamycin 10 mg/gm.) and Kenacomb* (Triamcinolone acetonide 1 mg/gm., neomycin 2.5 mg/gm., gramicidin 0.25 mg/gm., and nystatin 100,000 units/gm.) both of which are greasy ointments and used in a similar fashion to the corticosteroid ointments.

(ii) Intralesional Injections of Corticosteroid

A method that has been used successfully in the treatment of a variety of dermatological lesions involves the injection of a corticosteroid drug directly into the lesions.[177,219,220] This approach which was perfected in the early 1960's offered encouraging results in treating inflammatory dermatological disorders, particularly when the dermatoses being treated occurred as localized lesions. Psoriasis has been the condition which has apparently benefited substantially from this form of therapy.

The therapeutic effect of the corticosteroid is probably due to its anti-inflammatory action. This intra-lesional method delivers a high but localized concentration of corticosteroid to the tissues whilst minimizing the systemic effects that may accompany oral or parenteral administration.

The corticosteroid of choice would appear, from a review of the literature, to be triamcinolone acetonide.

* Squibb

In order to provide a high concentration of active drug at the site of the lesion when an intralesional injection is given, it is necessary to use a suspension which is relatively insoluble.[215] Soluble preparations are not suitable since they rapidly disperse, producing systemic effects with no local benefit.[220]

Urbanek and Cohen[215] were the first to report the use of intralesional injections of triamcinolone acetonide to give some relief to a patient with extensive oral ulceration occurring in cicatricial pemphigoid. Their technique involved the intradermal injection of triamcinolone acetonide around ulcerated lesions every fourth day for thirty-seven days until the ulcers healed. Some dubiety must be cast on this technique because, as discussed previously, it is unwise to use corticosteroids on ulcerated tissue as healing will almost certainly be delayed and indolent ulcers will persist.

(ii)(a) Technique

A suggested technique for the intralesional injection of triamcinolone acetonide 0.1 percent. The suspension should be delivered in a tuberculin syringe through a twenty-five gauge needle. As the injection may well be painful, a small quantity of local anaesthetic in the form of a regional block may make the procedure more comfortable. At any one injection site only 0.1 to 0.2 mls. of triamcinolone acetonide should be injected intradermally. The injection should be given around the lesion and not directly through it, so as to reduce the risk of

interposing an infective process. The injection should be given deep enough to avoid blanching but to produce a slight puffiness of the site.[177] The total amount injected at any one visit should be limited to 0.5 ml, and also to 1 ml. per week in order to prevent the development of Cushing's Syndrome.[215] It would appear that up to four weeks of this therapy is required,[177,215,219,220] although this period may well be empirical with the lesions healing prior to this length of time if injections were ceased.

The selection of lesions for this form of treatment is important. As discussed previously the use of topical corticosteroids on ulcerative lesions may well lead to the development of slowly healing indolent ulcers. It would therefore seem that localized vesiculo-bullous lesions are the lesions of choice. It is also important to realize that the use of intralesional corticosteroids will not prevent recurrence of lesions of cicatricial pemphigoid. Topical corticosteroid ointments are still required as an adjunct to this form of therapy with the advantage of intralesional injection lying in the fact that a higher concentration of corticosteroid is delivered to a localized area and remains in situ for a longer period.

3. Systemic Measures

In the case of severe, progressive cases of cicatricial pemphigoid that have been unresponsive to conservative treatment with topical corticosteroids it may be necessary to resort to the use of systemic therapeutic agents if only to prevent the disastrous sequelae of blindness and cachexia.

At the heart of therapy for such severe cases are corticosteroids administered systematically. Sometimes it is necessary to use cytotoxic agents - in combination with corticosteroids because of their purported immunosuppressive and steroid-sparing effects.

Immune diseases result from the interaction of an antigen and a factor the body produces that combines specifically with the antigen that produced it. The factor may be antibody, lymphocytes or both. After interaction of antigen with antibody or antigen with cell, a series of reactions occurs that usually results in inflammation.(3)

As has been discussed previously, the rationale for the use of corticosteroids lies in their ability to reduce inflammation, and also possibly to act as an immunosuppressive agent.

Cytotoxic agents such as methotrexate (folic acid antagonist), cyclophosphamide (alkylating agent) and azathioprine (purine analogue) are the drugs of choice used in cicatricial pemphigoid. These drugs were first introduced into clinical medicine for the treatment of malignant lymphoproliferative disorders such as Hodgkin's disease and various forms of leukaemia. They were used primarily for their ability to interfere with cell division. The demonstration that these drugs are also immunosuppressive coincided with an era of increased speculation that many chronic inflammatory diseases of unknown aetiology may have an immunological basis.(57) Accordingly, cytotoxic drugs such as azathioprine, methotrexate and cyclophosphamide have been used in a variety of such diseases; their immunosuppressive activity being the rationale behind their

use in cicatricial pemphigoid.

Systemic therapy with corticosteroids and/or cytotoxic agents offers the most effective and predictable control of cicatricial pemphigoid. The therapeutic goal of such therapy is to suppress the development of clinical lesions and the subsequent scarring whilst keeping the patient free of the complications of steroid therapy.

(i) Corticosteroids Alone

Cicatricial pemphogoid is generally less responsive and less self-limited than bullous pemphigoid; hence control is the aim of therapy. Since the disease is essentially benign, willingness of the patient and physician to accept occasional lesions will permit a lower dosage than would be possible with complete suppression.(187) This reduction in dosage is desirable as most of the patients with cicatricial pemphigoid are elderly and hence the hazards of high dosage corticosteroid therapy are increased.

A very significant advance in this aspect has been the use of alternate-day administration. Despite there being no evidence to suggest that corticosteroids given every other day changes the outcome of the disease, there is good evidence that this schedule significantly reduces the side effects.(3)

If systemic corticosteroids are used it is reasonable to commence with a loading dosage of between fifty and one hundred milligrams of predisone daily in divided doses.(132,158,178) Alternatively, triamcinolone (16 to 20 mg/day), dexamethasone (3 to 4 mg/day) or betamethasone (2 to 3 mg/day) may be used.(187)

This regimen should be continued until suppression of the majority of clinical lesions occurs. Following this a gradual reduction to a maintenance dose every other day may be achieved. Each patient will have an individual maintenance dose required to just suppress the development of new lesions and this may be as low as 5 mg/day of prednisone or its alternative.

(i)(a) Side Effects

The side effects of corticosteroids have been discussed in a previous section. It should be cautioned, however, that corticosteroids should not be given to elderly patients without strong indications. Adrenal axis suppression, glaucoma, subcapsular cataracts, delayed wound healing, gastrointestinal ulcerations, osteoporosis, and hypertension are known complications of systemic corticosteroid therapy that are even more of a concern with advancing age. (132)

(ii) Cytotoxic Agents Alone

The three drugs which have been used in the treatment of cicatricial pemphigoid are methotrexate, cyclophosphamide and azathioprine. The question arises whether these immunosuppressive agents, if administered alone, can equal the effect of corticosteroids in the management of cicatricial pemphigoid, and whether the side effects will be less severe and less frequent than in medium and high dose steroid maintenance therapy.

(ii)(a) Methotrexate

In 1970 Lever and Hashimoto[117] reported the use of methotrexate in the treatment of pemphigoid. They believed that the strong evidence in favour of an autoimmune aetiology of pemphigoid made it seem logical to employ an immunosuppressive drug such as methotrexate in its treatment.

Methotrexate was given intravenously or orally once a week; the intravenous route being preferable in the initial stages as larger doses were tolerable without the development of nausea. Prednisone (15 mg daily) exerted a protective effect against nausea and allowed the use of higher doses of methotrexate. The initial dose of methotrexate when given without prednisone was 24 mg and the dose was raised in increments of 5 mg to levels as high as 60 mg. In patients receiving maintenance treatment with prednisone the initial dose of methotrexate was between 40 and 80 mg and was raised to 100 mg if tolerated. Of the five patients treated by Lever and Hashimoto in this manner, four responded with all lesions clearing in one month.

The most commonly encountered side effect associated with the use of methotrexate is a depression of the white blood cell count.

(iii)(b) Cyclophosphamide

Brody and Pirozzi[27] have reported the only case of cicatricial pemphigoid to be treated with cyclophosphamide. The patient they reported had initially been treated with corticosteroids and azathioprine without resolution of ocular or buccal mucosal

lesions. A regimen of cyclophosphamide 50 mg twice daily gradually raised to 200 mg daily cleared all lesions.

The side effects of note are alopecia, mucosal loss, haemorrhagic cystitis and myelosuppression. Hence white blood cell counts and haemoglobin estimations are necessary on a regular basis if therapy with cyclophosphamide is being considered.

(ii)(c) Azathioprine

Azathioprine is generally considered to be a relatively mild cytotoxic agent with strong immunosuppressive activity and to be probably less hepatotoxic than methotrexate or cyclophosphamide.(58) The metabolite of azathioprine, 6-mercaptopurine, also has an additional non-specific anti-inflammatory action.(55)

One of the great advantages of azathioprine therapy over corticosteroids and other cytotoxic agents appears to be its ability to significantly improve the prognosis regarding vision in patients with ocular changes and therefore prevent blindness.(55)

Burton and Greaves(32) in a four year follow-up study of patients with pemphigoid being treated with azathioprine reported prolonged control of the disease. The recommended regimen for control of the lesions of pemphigoid has been a dose of 2.5 mg per kilogram of body weight per day. It remains as yet uncertain whether azathioprine in this dosage exerts its beneficial effect by suppressing antibody-mediated tissue injury in an anti-inflammatory capacity or whether it produces a true central immunosuppression.(32)

The known side effects of azathioprine therapy include nausea and vomiting, depression of bone marrow and gut mucosa, liver damage, cholestatic jaundice, drug fever and rashes. These side effects are, however, said to be rather uncommon.[58] Prolonged administration may also diminish the patient's resistance to bacterial and viral infections.

(ii)(d) Risk of Malignancy

The hazards of long term cytotoxic therapy must be balanced against their beneficial effects on the lesions of cicatricial pemphigoid.

It has been suggested that azathioprine might increase the risk of disseminated malignancy in elderly patients with cicatricial pemphigoid.[32] The rationale behind this supposition lies in the theory of immunological surveillance which states that the immune system destroys neoplasms as they arise in the body, and immunosuppressive therapy might be expected to be associated with an increased incidence of malignancy. There is, however, no convincing data available to support this theory.

Burton and Greaves[32] reported that two out of twelve patients in a prospective but uncontrolled trial died of cancer within two years after starting azathioprine therapy. They suggested that the risk of disseminated malignancy after suppression of immunosurveillance may be greater in patients with pemphigoid than in others because of the suspicion that the disease may occasionally be secondary to occult or overt malignancy. Even if there is no causal relationship between

cancer and pemphigoid few would dispute that occult malignancy is more likely to be present in elderly patients than in those from younger age groups, and patients with pemphigoid, being elderly, might be particularly at risk from immunosuppressive drugs. The controlled study conducted by Burton, Harman, Peachey and Warin,[33,34] in which patients were carefully followed for three years, showed no evidence of increased malignancy with azathioprine therapy. Van Dijk and van Velde[58] also found no evidence of malignancy in their study.

(iii) Corticosteroid/Cytotoxic Combined Therapy

Since a relatively long period is required before the clinical effect of the drug becomes evident, azathioprine is less satisfactory for the initial management of diffuse and rapidly progressive cases of cicatricial pemphigoid.[58] Under these conditions, high-dose corticosteroid therapy remains the standard treatment. As soon as the disease is under control, azathioprine can be added, permitting a lower steroid maintenance dosage. In some cases this drug can finally replace the corticosteroid.

In 1978 Burton, Harman, Peachey and Warin[33,34] reported on a controlled trial of azathioprine with prednisone versus prednisone alone in the treatment of pemphigoid. All patients received oral prednisone (30-80 mg daily) for one week to suppress new blisters. The control group continued to receive prednisone as dictated by their clinical state. The azathioprine group also continued with prednisone but in addition received azathioprine, 2.5 mg/kg body weight daily. The mean dose of prednisone received over a three

year period by the patients who were also receiving azathioprine was 45 percent lower than the mean dose received by patients receiving prednisone alone.

Similar results were also achieved by Lozada[120] when using azathioprine with prednisone.

Both studies showed that azathioprine can effectively enhance corticosteroid immunosuppressive activity, with satisfactory clinical efficacy and a marked reduction in side effects. The mechanisms by which azathioprine acts synergistically on prednisone to enable such low doses to be effective as yet are not well understood.

Two important factors arise from this discussion. Treatment with an immunosuppressant alone, such as azathioprine, during an acute stage of cicatricial pemphigoid has shown itself to be inferior to the combined treatment with a corticosteroid such as prednisone.[73] Also, cytoxic agents and corticosteroids are powerful drugs with already discussed serious side effects. Just as these two drugs act synergistically to be of greater clinical effect, the same may also be true of some side effects such as the risk of infection.[33]

(iv) Sulphones

The treatment with sulphones, although of great value in several dermatological disorders, is still quite empirical, and the mechanism of action is poorly understood. There has been, however, an unequivocal positive response in well established cases of dermatitis herpetiformis.[92]

Person and Rogers[158] recorded several patients with bullous pemphigoid who responded favourably in varying degrees to the administration of dapsone. They hence emphasised the efficacy of dapsone in the treatment of some patients with bullous pemphigoid. In a follow-up series[159] they found that five out of six patients, who had oral lesions of bullous pemphigoid, had their lesions controlled by the use of dapsone. Of note in particular was the fact also that patients with cicatricial pemphigoid of Brunsting-Perry type were successfully treated with dapsone, even in very chronic cases not responding to other forms of treatment.

On the basis of these findings Person and Rogers[158] suggested that trials of sulphones be carried out in patients with cicatricial pemphigoid. In 1982, Rogers,Seehafer and Perry[169] recorded the first series of patients who were treated with dapsone.

In this study, the authors sought an alternative form of anti-inflammatory suppressive therapy because of the problems of drug toxicity from systemically administered corticosteroids and immuno-suppressive agents amongst more elderly patients. Dapsone was the drug selected upon the basis of two previous studies.[158,159]

The indications for the use of dapsone therapy include severe disease activity, inadequate response to local or systemic therapy, or toxicity from systemic therapy.[159] The therapeutic objective of this study was to control active inflammation; reduction in, or absence of, erythema, oedema, induration, and symptoms being interpreted as control. Healing of old and failure to develop new erosions, bullae, and ulcers being also interpreted as control.

Of the twenty-four patients in this study, twenty (83 percent) had partial or complete control with mild to no inflammatory activity. A point of interest which appears common to all therapeutic measures is the fact that patients with ocular involvement require a longer period of time to obtain control with dapsone.

(iv)(a) Dosage

Dapsone therapy should be commenced at low doses (25 mgs. daily for 3 days, 25 mgs. twice daily for 3 days, 25 mgs. three times a day for 3 days, 50 mgs. twice daily for 3 days), then increased to the dose anticipated to provide control (75 mgs. and 50 mgs. daily for 7 days, and then 75 mgs. twice daily thereafter). By increasing the dosage slowly over a 19-day period, the side effects of dapsone therapy may be minimized. The continuation of low dose dapsone therapy alone or as adjunct to systemic corticosteroids and immunosuppressive agents is recommended.

(iv)(b) Side Effects

Several untoward side effects may accompany dapsone therapy. These include haemolysis and attendant anaemia, skin rashes, 'flu-like illness, and a decrease in haemoglobin level. These side effects, although worrying, were considered by the authors[159] to be mild compared to those associated with corticosteroids and immunosuppressives.

(iv)(c) Lesion Response

The lesions which show the most dramatic response are those of the superficial, anterior oral mucosa, such as gingival lesions, which are much less likely to scar.(159) Deep, ulcerated lesions require longer to control as do nasal, laryngeal, oesophageal, cutaneous, and genital lesions. Although ocular lesions require longer to demonstrate maximum benefit, the institution of dapsone therapy at an early phase of their development may well lead to a striking reduction in the effects of inflammation.(159)

(iv)(d) Mechanism of Action

The mechanism of action of dapsone remains unclear.(92,159) Several means by which dapsone exerts its effect have been postulated. High-dose, long-term therapy can suppress the Arthus reaction in the guinea pig.(209) Dapsone has been shown to inhibit the release of lysosomal enzyme in a similar way to corticosteroids.(12) Some authors have also postulated that dapsone modulates the alternative complement pathway.

Despite the still empirical use of dapsone, on the basis of the three studies in which dapsone has been used in patients with bullous and cicatricial pemphigoid, its remarkable effect in some of these cases requires that it be added to treatment modalities available for these diseases.

4. Surgical Measures

Surgery has not been a widely used mode of therapy in cicatricial pemphigoid, although the theoretical consideration of

replacing oral lesional tissue with skin that has a low propensity to develop lesions is attractive. Only a handful of published cases have described the excision of lesions and the placement of skin grafts.[76,132,151,192,194]

Lever[116] has distinguished two types of cutaneous lesions in cicatricial pemphigoid. One type of lesion consists of recurring eruptions of bullae, usually limited in extent, which heal without atrophy. The other type of lesion consists of areas of erythema, usually few in number and with a predilection to the face and scalp. The lesions result in atrophic scarring. The initial attempts at using split thickness skin grafts following lesional excision were made on the latter of these types of cutaneous lesions.[192,194]

Slepyan, Burks and Fox[192] described a patient displaying a massive non-healing erosive lesion affecting the major portion of the scalp. A split thickness skin graft from the uninvolved abdominal skin was applied to the scalp. The skin graft took well but approximately five weeks after grafting, a bullous eruption occurred in the donor site.

Sneddon[194] described a similar occurrence in a patient with a large ulcerated lesion on the arm. The lesion was excised and a split thickness graft taken from the thigh. The skin graft healed successfully but, as in Slepyan's case, the donor site developed a bullous eruption some three months later. This area was excised and covered with a skin graft from the adjacent thigh - healing occurred in both sites and no breakdown was observed at the donor site. A third grafting procedure for abdominal lesions was later

undertaken but once more the donor site showed a bullous eruption within three months. An interesting observation in the case presented by Sneddon[194] is the fact that at each separate graft donor site healing occurred, apparently normally, only to be followed by a breakdown some time later. He points out that there seems to be some deterrent to epithelialization present on the site of persistent blistering and that trauma to apparently normal skin, such as the removal of skin grafts may, however, initiate fresh blistering which in turn causes persistent ulceration.

The case presented by Hardy, Perry, Pingree and Kirby[76] describes a patient with nasal mucosal lesions. In this case a skin graft from the thigh to the nasal mucosa was employed to control an area of persistent haemorrhage and stenosis. This procedure left the nose symptom free, but the donor site subsequently developed bullous lesions. No mention was made as to whether this patient had existing skin lesions of cacatricial pemphigoid.

Skin grafting to replace bullous or scarred oral mucous membrane has only been twice reported.[132,151] In both cases the chief complaint of the patient was the inability to wear a lower denture because of severe pain and mucosal scarring. This scarring had led to a marked decrease in the depth of the mandibular buccal vestibule with resultant inadequate peripheral denture seal. In both cases it was decided that a split-thickness skin graft vestibuloplasty should be performed in order to provide a more suitable denture-bearing surface and to replace ulcerated and scarred tissue. In both cases skin was chosen as the graft

tissue. In these cases the grafted sites healed well and showed no further development of bullous lesions. No bullae or ulceration was noted in the donor site of either patient. It should be noted that in both patients the skin had never shown the presence of lesions associated with cicatricial pemphigoid.

The development of cutaneous lesions at sites of trauma (Koebner phenomenon) was originally observed in psoriasis but now may be equally applied to a disease such as cicatricial pemphigoid. This phenomenon was seen in the three separate cases of skin graft procedures already described.[76,192,194] It did not, however, occur in the other two cases described.[132,151]

The clinical picture of cicatricial pemphigoid varies considerably in extent of involvement. Patients with extensive oral involvement but minimal and preferably no skin lesions probably represent the best candidates for a split-thickness skin graft procedure.[151] The success of the procedure in patients with concurrent skin lesions would appear illogical and unpredictable as immune-complex formation has obviously occurred in the skin (whether it shows frank lesions or not). The use of palatal or buccal mucosa as donor tissue is for the same reason less likely to succeed because of the potential to develop lesions in the donor tissue. By removing the diseased mucous membrane and superficial connective tissue surgically, and replacing it with non-involved cutaneous tissue, a more favourable and predictable result should be achieved.

The use of skin grafts to selected areas in selected cases of cicatricial pemphigoid has definite merit and should not be

overlooked as a treatment modality, particularly in patients whose denture wearing ability has been reduced by the effects of painful ulceration and scarring.

5. Treatment of Ocular Lesions

The preceding discussion has resolved primarily around the treatment of lesions of cicatricial pemphigoid as they affect the oral mucosa. These treatment modalities may be extrapolated to encompass the other mucosal surfaces and skin. However, the treatment of the ocular lesions of cicatricial pemphigoid is difficult and somewhat limited and hence requires separate discussion.

As has already been discussed, the use of corticosteroids both topically and systemically is unsatisfactory in arresting the progress of ocular lesions in cicatricial pemphigoid. Indeed the untoward side effects of such treatment - particularly in topical form - may directly contra-indicate these measures. Repeated subconjunctival injections of corticosteroid suspensions in the bullous stage may help to retard the ocular lesions.[158] As has also been discussed, the use of cytotoxic agents such as azathioprine has proven to be of possibly the greatest benefit in arresting the ocular complications of cicatricial pemphigoid.

The early recognition of ocular changes and the prompt administration of therapeutic agents to arrest these changes will no doubt serve as a means of avoiding the use of artificial tear solutions, ocular inserts, contact lenses - all of which are difficult and time-consuming to use - and surgical procedures

(the results of which are unpredictable).

(i) Tear Substitutes

In approaching the treatment of a disease such as cicatricial pemphigoid as it affects the ocular apparatus causing a lacrimal deficient state, the replacement of the deficient secretions would seem to be a logical starting point.(110)

The term "dry eye" has been traditionally an inclusive one encompassing a number of diverse disease states. Based on the role different tear components play in establishing and maintaining a normal tear covering, two distinct types of dry-eye states have been distinguished.(111) These are the aqueous deficient and mucin deficient dry-eye states.

(i)(a) The Aqueous Deficient Dry Eye

The commonest type of dry eye state is kerato-conjunctivitis sicca, in which there is a deficiency of the aqueous component of tears, secreted by the main and accessory lacrimal glands, and an increase in mucin, secreted by the conjunctival goblet cells. There is a high degree of association of kerato-conjunctivitis sicca with collagen diseases such as rheumatoid arthritis.(111) Mucin, deprived of much of its natural solvent - the aqueous tears - gives rise to a viscous, stringy, scanty tear film.

(i)(b) The Mucus-Deficient Dry Eye

In contrast to kerato-conjunctivitis sicca, cicatricial pemphigoid is a condition in which the primary deficiency is of mucin. Mucin, spread by the action of the lids, adsorbs into the corneal surface and renders it wettable by tears.[111] Mucin deficient dry eyes are characterized by difficulty in maintaining a continuous precorneal tear film, despite adequate aqueous tear production. In mild cases this difficulty is manifested as an abnormally rapid breakup time of the tear film between blinks - less than ten seconds.[112] In more severe cases there are large areas of discontinuity in the tear film with underlying corneal and conjunctival dessication.

Cicatricial pemphigoid is an example of the mucin deficient dry eye state but particularly in those eyes with extensive destruction of normal conjunctival architecture involving both goblet cells and lacrimal gland ducts the two distinct types of dry eyes may coexist.[111]

(i)(c) Influence of Properties of Artificial Tear Solutions

Certain properties of solutions used in the treatment of any dry eye state influence the subjective response of patients.

pH: The normal pH of tears varies between 7.0 and 7.4. Solutions instilled into the conjunctival sac with pH below 6.6 and above 9.0 are associated with irritation.[130] The introduction of a buffering system ensures that a solution remains at approximately the pH of normal tears.

Tonicity: Instilling into the conjunctival sac solutions,the tonicity of which is markedly different from that of normal tears, is associated with a marked degree of irritation particularly in eyes affected by dry eye states.(110) Tonicity should range between 0.6 and 1.5 percent sodium chloride.(130)

Emollient Properties: In inflamed eyes relief is obtained with agents with soothing properties that lessen the friction between the dried surfaces of the tarsal and palpebral conjunctiva and the cornea.

Retention Time: The main limitation to the use of artificial tear solutions is their extremely short retention time in the conjunctival sac. Although increasing the viscosity of tear solutions has little effect on retention time (it may also cause crusting of the lid margin) agents such as gelatin, methylcellulose and other cellulose ethers have been employed to this end, the rationale being that the increase in viscosity would mean less rapid excretion.(110) Non-viscous dilute polymer solutions have also been used because of their film-forming properties over the ocular surface.(104)

Despite these efforts, the retention time obtained with current artifical tear solutions is simply inadequate in providing prolonged comfort for patients with severely dry eyes.

(i)(d) Treatment of Mucin-Deficient Dry Eye

In severe cases of cicatricial pemphigoid both aqueous and mucin components of the tear film are depleted. Introduction of aqueous solutions without mucomimetic properties into the eyes of

patients with ocular lesions of cicatricial pemphigoid, whilst introducing larger volumes of lacrimal secretion, will not effect the wetting of the corneal surface and dessication will continue, since the primary ocular wetting agent, mucin, is deficient or totally absent.[110,111] The ocular surface is hydrophobic and aqueous solutions will not cover this area. Treatment for eyes made dry by the effects of cicatricial pemphigoid must be directed towards introducing tear substitutes that possess mucomimetic properties.

No currently available artificial product completely satisfies the requirements for ocular wetting needed in the treatment of cicatricial pemphigoid. However, because mucin itself is a polymer, the search for constituents of artificial tear solutions that resemble mucin in their affinity for the ocular surface has been directed at the group of chemical compounds known as polymers.[110] However, solutions which contain polymers have been found to be satisfactory only in relatively mild cases of cicatricial pemphigoid dry eyes.[111] An acceptable artificial tear solution used in cases of cicatricial pemphigoid is Liquifilm* which contains polyvinyl alcohol (as a polymer) and methylcellulose.

* Allergan, California, U.S.A.

(ii) Ocular Inserts and Mechanical Devices

(ii)(a) Mechanical Devices

As has been discussed, the treatment of a lacrimal deficiency such as cicatricial pemphigoid requires a regular supply of fluid in the form of a tear substitute. The usual method of fluid supply

has been limited to the application of eye drops, self-administered by the patient as often as six to eight times an hour in order to avoid discomfort. This is obviously an inconvenient and bothersome procedure for the patient. The advantages of a mobile, self-contained system whereby fluid, perhaps combined with a medication, could be administered to the eye automatically and continuously are obvious. The problems of such a system, however, remain unresolved.

The modification of spectacle frames by incorporating small tubular reservoirs and a length of tubing acting to conduct fluid into the nasal corner of the eye, driven by gravity or small pumps has been discussed by Doane.[59] Despite the attraction of such devices they remain cumbersome and no report has described their use for patients suffering from cicatricial pemphigoid. With the advances made in biomechanical engineering such a device and treatment modality may, however, become a feasible reality. The application of fluid and medication at a constant rate at very low volume also has pharmacological advantages over the intermittent high-low dose profile of drop delivery.

(ii)(b) Ocular Inserts

The technology of drug delivery systems took on two revolutionary approaches in the early 1970's [154] - the delivery of medication directly to target organs, and the systemic delivery through skin and mucous membranes, using drug-laden devices that are programmed for precisely controlled release. One of the organ systems that lends itself readily to both approaches is the eye.

The concept of the medicated ocular insert was the object of renewed interest with the advent of contact lenses.(154) These devices were drug-impregnated polymeric membranes (small, soft, flat discs) which were inserted by patient or physician into the lower cul-de-sac. They remained until predetermined spontaneous dissolution occurred. Although no reports have been made of their use in patients with ocular lesions of cicatricial pemphigoid, their use has been advocated for the patient with mucin deficient dry eyes, and future research into this field may be warranted.

The advantages of the ocular insert system are obvious. The constant-rate release of ocular medication insures that the patient receives adequate therapy not only during the waking hours but also through the night when he might otherwise be inconvenienced by having to administer drops. The devices are apparently well retained and tolerated, non-toxic and clinically effective in treating disease with less drug and fewer side effects compared to the other forms of applying medication to the eyes.(154)

(iii) Contact Lenses and Shells

Although they seem little able to prevent the progression of the conjunctival lesions, contact lens therapy has a definite place in the treatment of cicatricial pemphigoid.(10) In the more severe cases of the disease hydrophilic lenses used in combination with artificial tear solutions have proved very useful.(111) Unfortunately many of the severe cases of cicatricial pemphigoid have excessive symblepharon formation, which makes lens

fitting very difficult if not impossible.

Contact lenses afford a great advance, both optical and therapeutic. They improve visual acuity, protect the globe from drying (by retaining moisture), separate the conjunctival surfaces and afford a mechanical barrier to irritation of the globe and cornea by ingrowing lashes (trichiasis).[165,206] They also improve the patient's comfort.

Ridley[165] pointed out that the contribution contact lenses make, apart from improved visual acuity, is to hold open the fornices preventing contraction and adhesion in the subacute stage. As a rule they cannot be worn in the acute stage of the disease, but when quiescent the lenses should be fitted and worn for periods as long as possible.

If the eyes have any natural tear secretion then contact lenses may afford this as being adequate by preventing evaporation from the ocular surface. If the eye is dry use of contact lenses in conjunction with an artificial tear solution, as pointed out, may be beneficial.

Ridley[165] believed that once all-day wear is established, any discharge ceases, the cornea often clearing steadily over several months, vascularization subsides, the eye becomes quiet and the fornices reform to a considerable extent by re-expansion of the contracted conjunctiva because the globe is now permanently wetted. In general he also stated that old people with active lesions and wet eyes are difficult to fit and tend to do badly - visual acuity often being good and so no immediate benefit being gained. Patients in the quiescent stage following the disease

in early life - and usually with dry eyes and corneal involvement - do very well.

Apart from the above accounts of the uses of contact lenses in cicatricial pemphigoid there has been no literature on the subject for some years. This no doubt corresponds to the advent of the use of azathioprine to halt the ocular disease in cicatricial pémphigoid at an early stage, thus much diminishing the need for such forms of therapy.

(iv) The Role of Surgery for Ocular Lesions

If the ocular lesions of cicatricial pemphigoid are allowed to progress the ultimate effect of symblepharon formation is to unite the lid and globe firmly together and to invert, by secondary contraction, the lashlines so that the lashes irritate the cornea and produce ulceration. Coincidentally vascular tissue spreads across the cornea and obstructs vision. The lacrimal ductules and orifices of the lacrimal puncta are usually occluded by scar tissue and finally xerophthalmia occurs leading to total opacification of the cornea with keratinization and absolute fixation of lids and globe.

Rycroft[174] has made the comment that fortunately for surgeons the pathology of the ocular lesions shows that they are largely superficial and occupy a distinct plane. This statement tends to paint a rather simplified picture of the surgery for ocular lesions of cicatricial pemphigoid. This is indeed not so as the disappointing results tend to show. Indeed Bedell[18] aptly points out that the tendency is to report the success of an

operation without waiting for the disappointing end-result.

It would appear logical, from previous discussion, that any form of surgery to the ocular apparatus damaged by cicatricial pemphigoid constitutes physical trauma. As has been stated previously, the Koebner phenomenon in cicatricial pemphigoid is a common occurrence which would seem to indicate that any surgical procedure, even of a minor nature, may predispose to the development of new lesions and further scarring.

(iv)(a) Superficial Keratectomy

This procedure is undertaken to clear off redundant and excessive adventitious vascular tissue from the surface of the cornea.

(iv)(b) Fornix Incision

The primary objective of fornix surgery is to allow lid closure and to permit the fitting and retention of contact lenses. Symblephara are simply divided and no attempt is made to reconstruct the fornices as the final result will be worse than the initial condition by virtue of increased contracture.

The most important principles to be observed when contemplating surgical measures are to be as conservative as possible, in all cases to postpone surgery whilst the disease is in an active phase, and to cover all patients with an intensive regimen of corticosteroid therapy.[206] The rationale being that surgical intervention is capable of initiating new lesions in and around

an operative site.

Rycroft[174] warned that in earlier years it was his custom to carry out extensive reconstruction of the conjunctival fornices by free mucous membrane grafts but it was clear that the result of this surgery merely aggravated the vascularization and led to further cicatrization with complete failure.

Several conservative surgical procedures have been advocated for use in the early or moist stage of cicatricial pemphigoid as it affects the eyes.[174,206]

(iv)(c) Transcutaneous Linear Tarsectomy

This procedure, carried out on the upper and lower lids, aims to evert the lashes from the cornea thus reversing entropion and helping prevent trichiasis.

(iv)(d) Strip Peritomy

The result of this procedure is that a bare avascular area surrounds the cornea and is a temporary barrage to the ingrowth of adventitious conjunctival vessels. This is only a temporary measure because later the conjunctiva grows across. However, it may leave time for the corneal lésions to heal.

6. Prognosis

The prognosis of cicatricial pemphigoid is generally quite good as long as the complications related to scarring and fibrosis can be prevented.[132] These two untoward processes, in the case of advanced ocular lesions, may lead to impairment of vision and, in

some cases, eventually to blindness. In other cases, but less commonly, fibrosis may cause stenosis of the larynx and oesophagus with consequent debilitating effects. The same is true if extensive scarring occurs in the oral mucous membrane. This can make the wearing of dentures and maintenance of nutrition most difficult.

With the advent and use of powerful systemically administered immunosuppressive drugs, the unfortunate problems described above may be averted. Despite these measures, however, cicatricial pemphigoid shows little tendency for remission.[158] In most cases the disease persists over many years showing periods of exacerbation and partial remission.

With reasonable dental care and ophthalmological attention and therapeutic maintenance disease control,the complications can be prevented and the periods of remission sustained for long periods with the majority of patients satisfied to endure the development of occasional lesions.

CONCLUSION

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Vesiculo-bullous disorders as they affect the skin and mucous membranes have been recognized for many centuries and indeed reference to a number of them was clearly made by Hippocrates. It was not, however, until the middle of the twentieth century that Lever defined cicatricial pemphigoid as a disease entity in its own right, and so was no longer to be considered as a variant of the pemphigus group.

The definition of cicatricial pemphigoid on clinical, microscopic and immunopathological grounds has enabled its differentiation from a number of other disorders which it closely mimics. These include pemphigus vulgaris which although being remarkably similar in its clinical appearance, has a vastly different prognosis as far as life expectancy is concerned.

The clinical features, light and electron microscopic appearances, and the immunopathological findings, form the basis upon which cicatricial pemphigoid is recognized and diagnosed. Certainly an important step towards fully understanding the aetiology of cicatricial pemphigoid has occurred since the application of various immunofluorescent techniques to characteristic lesions has demonstrated the presence of antigen-antibody complexes at the basement membrane zone of the mucosa.

The inclusion of cicatricial pemphigoid in the spectrum of auto-immune diseases has led to a rationalization of treatment modalities as far as the use of powerful corticosteroid and cytotoxic agents is concerned. Care of the patient's natural and artifical

dentition are the primary treatment concerns of the dental surgeon. Restricting the development of new lesions and preventing the devastating effects of ocular and laryngeal lesions by the judicious use of parenterally adminstered powerful drugs are the foremost responsibilities of the physician and clinical immunologist. The treatment of cicatricial pemphigoid, although still basically empirical, therefore involves a medical team approach if all the problems associated with this disease are to be recognized and subsequently dealt with.

The endeavours of future research will be directed towards discovering the cause of cicatricial pemphigoid. Undoubtedly the refinements which will be made in immunopathological methods and the use of the electron microscope to more precisely detect and localize antigen-antibody complexes within the basement membrane zone will lead to a fuller understanding of the disease processes of cicatricial pemphigoid.

Dental surgeons and physicians who are aware of and recognize the earliest signs of cicatricial pemphigoid will be able to institute treatment before the more debilitating features of this disease become established in their patients.

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